SYNTHESIS CHARACTERIZATION AND CATALYTIC APPLICATIONS OF NEW NICKEL(II) AND PALLADIUM(II) BIS(HYDROXYMETHYLOXAZOLINE) COMPLEXES IN CROSS COUPLING AND C-H ARYLATION REACTIONS

BY

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Dedicated to my parents

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To all my friends and relatives, thanks for your prayers and well wishes

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LIST OF ABBREVIATIONS

BOX	:	Bis(oxazoline)
BOX-OH	:	Bis(hydroxymethyloxazoline)
d	:	doublet
DPEphos	:	Bis-[2-(diphenyphosphino)phenyl]ether
DMF	:	dimethyl formamide
DMSO	:	dimethyl sulfoxide
EA	:	Elemental analysis
EtOAc	:	ethyl acetate
FID	:	Flame ionization detector
FTIR	:	Fourier transform infrared
GC	:	Gas chromatography
GC-MS	:	Gas chromatography-mass spectroscopy
h	:	hour
IR	:	Infra red
J	:	coupling constant
Me	:	Methyl
Mes	:	Mesitylene or 1,3,5-trimethylbenzene

NHC : N-heterocyclic carbenes

Ni-BOX : Nickel(II)-bis(oxazoline)

Ni-BOX-OH : Nickel(II)-bis(hydroxymethyloxazoline)

NMR : Nuclear magnetic resonance

OAc : acetate ion

Pd-(BOX-OH) : Palladim-bis(hydroxymethyloxazoline)

$Pd_2dba_3 \cdot CHCl_3$: Dipalladium tris(dibenzylideneacetone)chloroform complex

Pd-Pyr-OX-OH : Palladim(II)-oxazolinylpyridine

Ph : phenyl

OPh : phenoxy

OX-COOH : oxazolinyl benzoic acid

Phos : phosphine

ppb : part per billion

ppm : part per million

psi : per square inch

Pyr-OX-OH : oxazolinylpyridine

r.t. : room temperature

s : singlet

t : triplet

t-Bu-Amphos : 1-trimethylammonium-2-(di-t-butyl)phosphine)ethane chloride

ABSTRACT

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Herein, we carried out the synthesis of new bis(hydroxymethyloxazoline) ligands (BOX-OH-1 and BOX-OH-2), new pyridinyloxazoline ligand (Py-OX-OH) and benzooxazolinebenzoic ligands (OX-COOH). The synthesis of palladium(II) bis(hydroxymthyloxazoline) complexes [Pd-(BOX-OH)-1 and Pd-(BOX-OH)-2] and palladium(II) pyridinyloxazoline complex [Pd-Py-(OX-OH)], nickel(II) bis(hydroxymethyloxazoline) [Ni-(BOX-OH)-1] and nickel(II) bis(oxazoline) [Ni-BOX-A] were also successfully accomplished. The new BOX-OH and Py-OX-OH ligands, Ni-BOX, Pd-Py-(OX-OH) and Pd-(BOX-OH) catalysts were characterized using various analytical and spectroscopic techniques. The established X-ray crystal structure of the complex [Pd-(BOX-OH)-1] showed that the two nitrogen atoms of the two oxazoline rings in the bidentate ligand were bound to the palladium metal atom and the two halide on the palladium atom were in a distorted square planar geometry. The Pd-(BOX-OH) catalysts were effective in the Suzuki-Miyaura coupling reactions of aryl boronic acids with aryl iodides and aryl bromides in neat water, iodides, aryl bromides and aryl chlorides in DMF:H_2O (1:1). Mizoroki-Heck coupling reactions of aryl halides with terminal alkenes, and copper free Sonogashira coupling reaction of aryl halides with terminal alkynes were also effectively catalyzed by these catalysts. We considered

various derivatives of aryl boronic acids, aryl halides, alkenes and alkynes with a wide range of functional groups on the as substituents. While the Ni-BOX-OH-1 catalyst and $Ni(OAc)_2.4H_2O$/BOX-OH-1 catalytic system each was considered for the catalyzed C-H arylation reaction of unactivated arenes. The Pd-(BOX-OH)-1 complex was also active in the alkoxycarbonylation and aminocarbonylation reactions of aryl iodides. The Pd-BOX-OH catalysts were found to be highly air and moisture stable.

ملخص الرسالة

الاسم الكامل: ابراهيم مونكايلا عبدالاهي

عنوان الرسالة: توليف وتوصيف وتطبيقات معقدات نيكيل وبلاديوم-بس أوكسازولين جديدة كحفازات في تفاعلات الإقتران وأريلة الكربون-الهيدروجين

التخصص: الكيمياء

تاريخ الدرجة العلمية: مايو ٢٠١٦

تم - في هذه الدراسة – إجراء توليف متصلات هيدروكسي ميثيل بس أوكسازولين جديدة (بوكس-هيدروكسي-1 و بوكس-هيدروكسي-2) ومتصلة بيريدل أوكسازولين جديدة (بي-أوكس-هيدروكسي) ومتصلة بنزأوكسازولين بنزويك أسيد (أوكس-أسيد). كما تم أيضا توليف معقدات بلاديوم-هيدروكسي ميثيل بس أوكسازولين (بلاديوم- بوكس- هيدروكسي-1 و بلاديوم- بوكس- هيدروكسي-2) ومعقدات البلاديوم- بيريدل أوكسازولين (بلاديوم- بي-أوكس-هيدروكسي) و معقدات نيكيل-هيدروكسي ميثيل بس أوكسازولين (نيكيل- بوكس- هيدروكسي-1) ونيكيل بس اوكسازولين (نيكيل - بوكس-أ). تم توصيف المتصلات هيدروكسي ميثيل بس أوكسازولين و بيريدل أوكسازولين و بنزأوكسازولين بنزويك أسيد ومعقدات بلاديوم- هيدروكسي ميثيل بس أوكسازولين وبلاديوم-بيريدل أوكسازولين ونيكيل- هيدروكسي ميثيل بس أوكسازولين ونيكيل بس اوكسازولين باسنخدام مختلف التقنيات التحليلية والطيفية. تظهر هيكيلية المعقد بلاديوم- بوكس- هيدروكسي-1 والمنشأة باستخدام الأشعة السينية بوضوح أن ذرات النيتروجين الإثنتين في حلقتي الأوكسازولين تتصلان مع ذرة البلاديوم بشكل ثنائي وأن ذرتي الهاليد هما على شكل مربع مستو مشوه. كانت محفزات البلاديوم- هيدروكسي ميثيل بس أوكسازولين فعالة في تفاعل اقتران سوزوكي - مايورا لحمض البورونيك مع أريل اليود والبروم في الماء النقي، وأريل اليود، البروم والكلور في الماء وثنائي ميثيل الفورم أميد بنسبة (1:1). كما تم تحفيز تفاعلات الاقتران ميزوروكي-هيك لهاليدات الأريل مع

الألكينات الطرفية، والخالية من النحاس وتفاعل اقتران هاليدات الأريل مع الأمكانيات الطرفية بشكل فعال باستخدام هذه المحفزات. وأخذنا في الإعتبار مشتقات مختلفة من الأحماض أريل البورون، هاليدات الأريل والألكينات والألكاينات مع مجموعة واسعة من المجموعات الوظيفية على شكل بدائل في التفاعلات. في حين اعتبر حفاز نيكيل- بوكس- هيدروكسي-1 و نيكيل- بوكس- هيدروكسي-1/أسيتات النيكيل رباعية التميوه كنظام تحفيزي في حفز تفاعل أريلة الكربون- الهيدروجين للأرينات غير المنشطة. كان حفاز البلاديوم- هيدروكسي ميثيل بس أوكسازولين 1 فعالا أيضا في تفاعلات الكربنلة الكحولية والكربنلة الأمينية لأريل اليود. كما وجد أن محفزات البلاديوم- هيدروكسي ميثيل بس أوكسازولين هي مستقرة بشكل كبير في الهواء والرطوبة.

CHAPTER 1

INTRODUCTION

1.1 General Introduction

In the last decades, catalysis became the most suitable route for the synthesis of important compounds, with high selectivity, mild reaction conditions, improved yields, and reduced cost. Carbon-carbon (C-C) bond formation is among the most highly regarded processes in synthetic organic chemistry which finds applications in majority of chemical industries for the production of new monomers, intermediates for petrochemical, pharmaceutical, polymer and dye industries. Originally, C-C bond forming reactions required rigorous reaction conditions and has a low tolerance to functional groups. The development of transition metal-catalysis allowed for much more selective, mild conditions for the formation of C-C bonds. Suzuki, Sonogoshira, Heck and Negishi coupling reactions are among the carbon-carbon bond forming reactions that are effectively catalyzed using transition metal complexes. Cross-coupling reactions are basically distinguished by the coupling of an organic electrophile with organic nucleophile and catalyzed by metal complexes. The organic electrophiles are mostly the organic halides such as iodobenzene, bromobenzene and chlorobenzene and their derivatives. The organic halide may bear any halogen or other similar leaving group denoted as "X" with C-X hybridization of SP- i.e. C≡C-X, SP^2- i.e. C=C-X, or SP^3-hybridized carbon i.e C-C-X. However, most research focus on SP^2 C–halogen bonds e.g. aryl halides, which might be due to the availability of

numerous important complex compounds containing diphenyl derivatives. Several reactions using organometallic carbon nucleophiles have been developed, these reactions are very important in synthetic organic chemistry. Examples of some of these reactions are given below with the corresponding organometallic species in parenthesis: Stille (organotin), Suzuki (organoboron), Kumada (Grignard reagents), Hiyama (organosilicon), Negishi (organozinc), and Sonogashira (in situ generated acetylide anions). The common aspect to these cross-coupling reactions is obviously the mechanistic steps involved, which start with the oxidative addition of the organic halide onto the organometallic specie, followed by transmetalation of the nucleophilic carbon, and finally reductive elimination to form the product. Although, Heck coupling of aryl halides with alkenes involves the migratory insertion/β-hydride elimination sequence instead of reductive elimination in the principal bond-forming mechanistic step, it also falls into this class of reactions.

1.2 Bis(oxazolines)

Bis(oxazolines) have two oxazoline rings and a spacer separating the two rings, which could either be aliphatic or aromatic moiety. These ligands have greatly received attention in asymmetric catalysis and in coordination chemistry in the last few years [1, 2]. In the last two decades, C_2 symmetry bidentate bis(oxazoline) compounds were discovered to be useful in asymmetric catalysis leading to high enantioselectivities [3]. Very good yields were obtained from the synthesis of various oxazoline derivatives from amino alcohols and nitriles. The fact that this synthetic route has a general applicable experimental procedure, simplicity in operation, readily available starting materials, and the presence of the many functional groups handled in many of the synthesis of the

oxazolines derivatives have promoted their synthesis for various applications [4]. The synthesis and full characterization of nickel(II) and palladium(II) complexes with chiral bis(oxazoline) ligands have been described in the literature as shown below (labeled A, B and C). The coordination behavior of these ligands through the N,N donor site, with emphases on the variation of the oxazoline moieties relative position on the phenyl spacer has been studied. These were used to study the N,N-coordination behaviors, and the application in C_{aryl}–H bond activation was studied as well [5]. They are very important with wide application potential, as they are easy and flexible to synthesize, and give excellent selectivity [6] and have the ability to coordinate with a large variety of metals [2], and for these, several BOX ligands have been synthesized and evaluated for various catalytic applications.

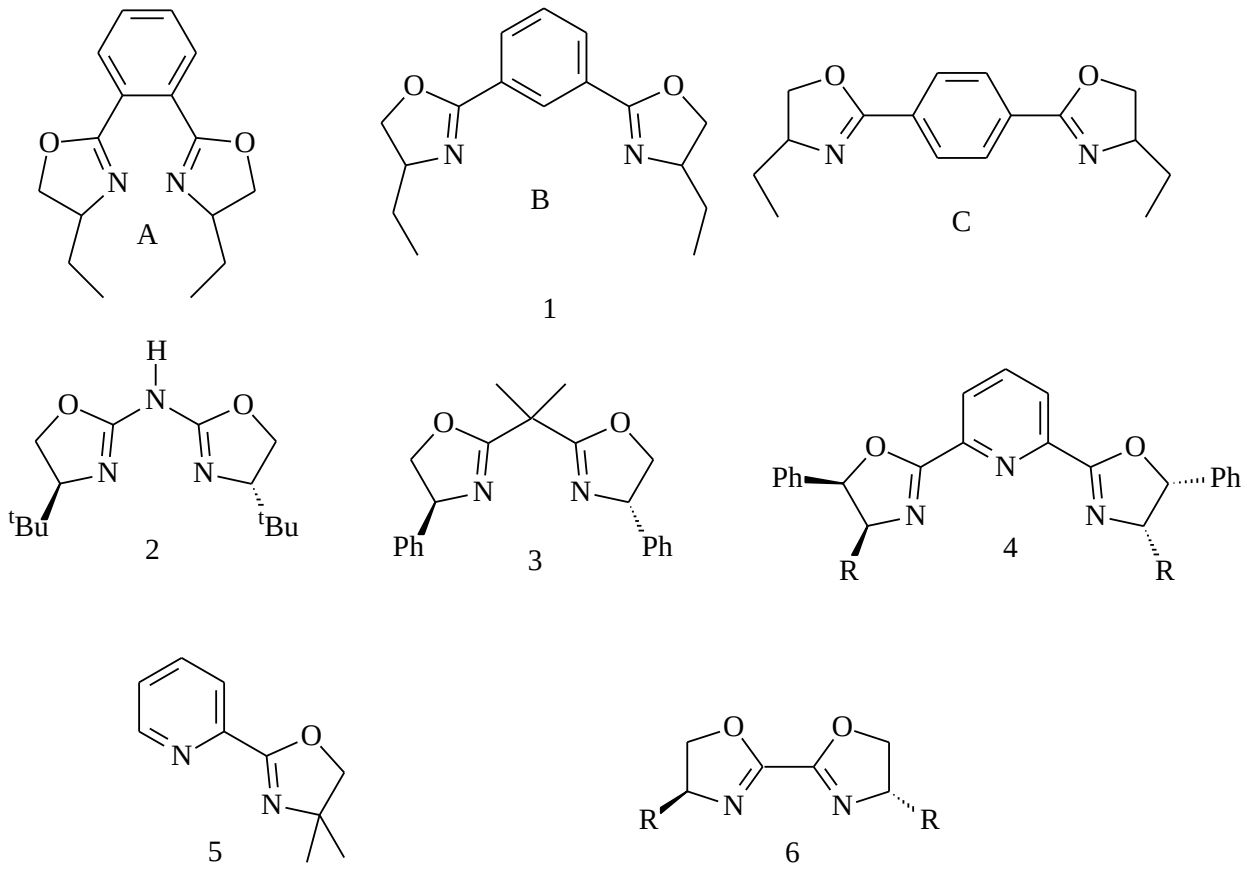


Figure 1: Some examples of bis(oxazoline) ligands 1 [5]; 2 [7]; 3 [8]; 4 [9]; 5 [10] ; 6 [11].

A chelating tridentate 2,6-bis(oxazoline) ligand was employed to retard undesirable β-hydride elimination which requires a vacant site for coordination, fortunately blocked by this ligand and also assists coupling of secondary electrophiles with vinyl or aryl boronic acids [12] and other aryl substrates [13]. Also, bis(oxazoline) ligand was reported to induce a very excellent enantioselectivity to the asymmetric acyl reductive coupling reaction [14]. A general method for the synthesis of BOX complexes was reported few years later [15], and interestingly, two communications were published in the journal of American chemical society in 1991, on asymmetric cyclopropanation of alkenes using chiral Cu(I)-BOX [16] and on enantioselective Diels-Alder reaction using chiral

Fe(III)-BOX [17] complexes as catalysts. Since then, a substantial number of BOX ligands and their metal complexes have been synthesized and evaluated. For appropriate understanding of what BOX is, there is a need to give an insight into the structural diversity of BOX ligands. A few examples are shown in Figure 1 and more details on BOX can be found in related reviews [2,18].

Nickel catalyzed Negishi reaction found promising activity with Pybox-ligands in enantioselective cross-coupling reactions of alkyl electrophiles, while Hiyama and Suzuki reactions were found to be favored with 1, 2-diamine ligands [19].

A novel coupling method was reported for the first time using readily available bis(oxazoline) ligands used alongside to alkyl electrophiles (α-bromoketones) for the coupling reaction. They observed that Kumada coupling proceeds in desired yield and enantioselectively in the presence of a suitable C2-symmetric bis(oxazoline) ligand [20-21].

The development of hydrophilic ligands has received a great attention especially using phosphine ligands. These phosphine ligands have made significant impact for the role they played in the progress of homogeneous catalysis over the years. On the other hand, the oxidation stability of nitrogen ligands makes them more promising than phosphine for catalytic applications conducted in conditions favoring oxidation. Hence, nitrogen-based ligands have been explored extensively as ligands and have played key role in many catalytic processes. Furthermore, there are numerous number of possible chiral ligands that could be synthesized from chiral diamines compounds that are readily available. Thus, reports on nitrogen coordinated ligands family is growing day by day, gaining popularity. 1,10-Phenanthroline and 2,2’-bipyridine ligands have been widely applied as

nitrogen ligands in the fields of homogeneous catalysis and in coordination chemistry. To make these ligands water soluble, they are sulfonated to mimic the water soluble phosphine ligands. However, unlike the phosphine ligands which are much easier to make, the nitrogen ligands are very difficult to synthesize; the pyridine ring is deactivated further to electrophilic sulfonation reaction as soon as the nitrogen is protonated, and hence very rigorous conditions are employed. The electrophilic sulfonation of 2,2′-bipyridine was carried out in 30% oleum for 1day at 220 °C. Alternatively, it was heated in fuming sulfuric acid at 300 °C for 10 h to give the 5-sulfonated product labeled (D (i)) in modest yields (Figure 2) [22]. The Sulfonation of 1,10-phenanthroline on the other hand was carried out by heating it at 365 °C in the presence of ammonium hydrogensulfate, producing a mixture of 3-sulfonated-1,10-phenanthroline (E (ii), with 4% yield), 5-sulfonated-1,10-phenanthroline (E) with 30% yield of the desired products [23].

In the case of pyridine, the electronic nature of the ligand was altered by including the water-solubilizing group directly on the ring. However, in order to avoid this step, the ionic substituent is separated by an alkyl chain from the pyridine ring e.g. ligand F (Figure 2) which was applied in Heck and Suzuki coupling reactions [24] and showed promising results.

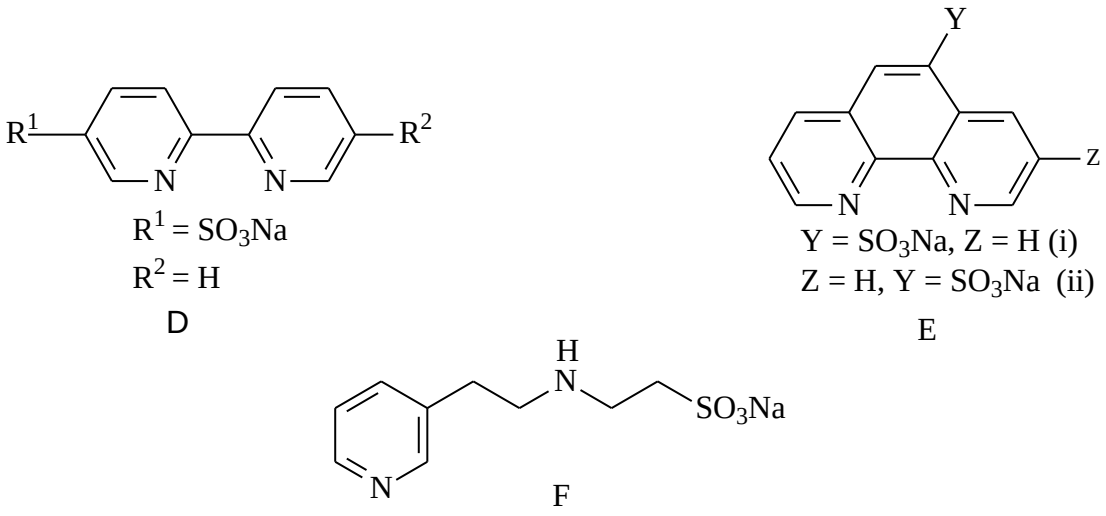


Figure 2: Example of some water soluble Nitrogen-based ligands applied in coupling reactions

The successful Sonogashira reactions of aryl bromides with terminal alkynes catalyzed by t-Bu-Amphos/$Pd(OAc)_2$ in aqueous phase has been described. Coupling reactions of both activated and deactivated aryl bromides were allowed by the t-Bu-Amphos ligand (Figure 3) under mild conditions, with some level of tolerance to some degree of steric bulk on the aryl bromide [25].

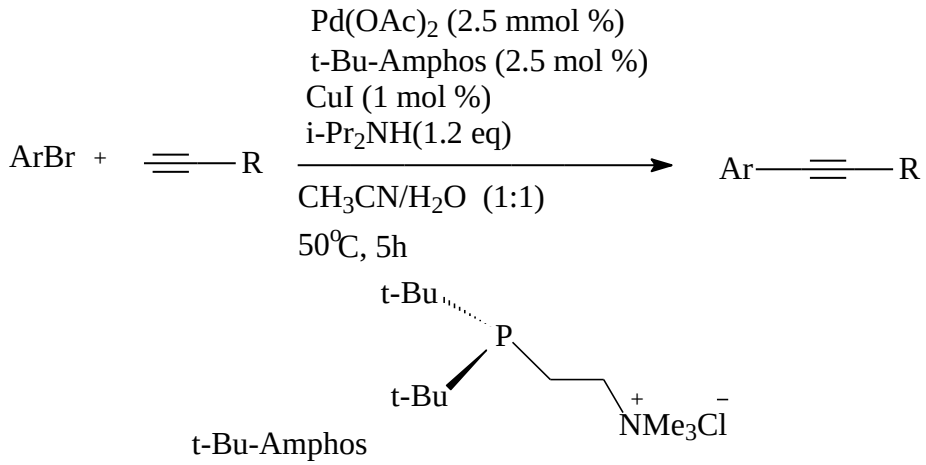


Figure 3: Synthesis of alkynyl arenes catalyzed by t-Bu-Amphos/$Pd(OAc)_2$ catalyst system

In general, the introduction of polar groups on ligands, including diimine ligands, can make them water soluble. Common groups include sulfonates, carboxylates, ammonium, phosphonium, and hydroxyl giving rise to the water-soluble derivatives [26].

The increasing advancements in the field of catalysis have led to a continuous increase in the demand for specially designed catalysts. Water-soluble ligands are very essential in water soluble complexes and are currently being intensively investigated. The advantages they have cannot be over emphasized. Water-soluble complex elegantly allows the complete separation of the product from the reaction medium, specifically from the catalyst. It may have high activity and high selectivity hence having the advantages of both homogeneous and heterogeneous catalysts. The synthesis of the numerous water-soluble ligands led to the development of the appropriate catalysts for specific reactions of various types. A significant progress has been achieved in the industrial hydrogenation and hydroformylation applications pointing out the wide scope of this group of catalysts. Moreover, rhodium complexes have been applied at Hoechst AG in Oberhausen, Germany, as water-soluble catalytic systems, which led to the production of 300,000 tons of butyraldehyde annually, thereby demonstrating the industrial significance of the idea of metal complex-catalyzed reactions in two-phase aqueous systems. Another important aspect is the recycling ability of the catalyst; this gives the overall efficiency in operation of catalytic processes. Using the two-phase systems, the noble metal catalyst can be efficiently and economically recycled without significant loss in activity.

In addition, the field of water soluble transition metal complexes could open up unique applications in biochemical reactions. In the near future, the priority in catalysis research may be tuned towards the screening and application of metal complexes used as catalysts

that are physiologically well matched, inexpensive, with environmentally friendly solvent such as water [27].

1.3 Metal-bis(oxazoline) complexes

Palladium complexes have been extensively employed in the cross coupling reactions [28] while nickel complexes have been used in arylation reactions under mild conditions [29]. Palladium-(bis(oxazoline)) complexes have shown promising activity in catalyzing coupling reactions (Suzuki–Miyaura, Sonogashira, and Mizoroki–Heck reactions) with various substrates [30]. Furthermore, it was reported that bis(oxazoline) (BOX) ligands are necessary for carbonylation of propargyl acetates, a tandem carbonylative cyclization, while in the absence of BOX, the reaction does not go to completion [31]. Based on these studies, Kato et al. concluded that these BOX ligands increase the π-electrophilicity of palladium(II) complexes and therefore the coordination of the second triple bond to palladium become more feasible which leads to the tandem reaction. Interestingly, the palladium-BOX complexes have been found to be strongly active for the carbonylation of alkynes. Just two years after, Kato et al have reported an intermolecular methoxycarbonylation of terminal alkynes catalyzed by palladium(II) bis(oxazoline) complexes [32].

Some systems were reported to show good catalytic activities in various coupling reactions; Suzuki–Miyaura [33], Mizoroki–Heck [34], and copper-free Sonogashira [35-36] coupling reactions. However, more recently, some novel palladium-bis(oxazoline) complexes based catalytic systems were developed in our laboratory for cross coupling reactions using mixed solvents (water - organic solvent) and under aerobic conditions. These newly synthesized palladium-bis(oxazoline) (Pd-BOX) complexes were

characterized fully with the help of various spectroscopic techniques and their molecular structures were confirmed using X-ray structure analysis [37]. The bis(oxazoline) ligands have substituents on the oxazoline rings in very close proximity to the donor nitrogen forming metal chelate complexes that are structurally constrained. Hence, the high catalytic activity and strong directing effect of the catalysts was maintained [30,38].

The unactivated arenes in the presence of a nickel catalyst and 1,10-phenanthroline, as a ligand, undergo direct C–H arylation with aryl halides under mild conditions, which indicates the potential of the nickel nitrogen based complexes for practical application purposes [39]. Nickel catalyzed oxidative cycloaddition of aromatic amides to alkynes have been carried out and was observed to be highly regioselective. The C-H at the ortho position is selectively activated in this reaction to give the cycloaddition product [40]. Heteroaromatic C-H activation is of great significance as it leads to important target molecules including natural product, pharmaceuticals and functionalized materials. Nickel catalyst have efficiently been used for heteroaromatic C-H activation in pyridine, imidazole, heteroarenes and azoles which are important ring precursors usually found mostly in bioactive compound of high value [41]. Pyridine alkylation has been selectively achieved on C-4 in a cooperative catalysis using an N-heterocyclic carbene ligand and a nickel/Lewis acid [42].

As mentioned above, the synthesis and characterization of new palladium–bis(oxazoline) (Pd–BOX) complexes have been reported by our research group**.** These complexes were applied in catalytic reactions such as Suzuki–Miyaura, Mizoroki–Heck and Sonogashira coupling reactions. A high catalytic activity was observed towards numerous C–C coupling reactions with various aryl halides, aryl boronic acids for Suzuki–Miyaura,

alkenes for Mizoroki–Heck and alkynes for Sonogashira coupling reactions. The reaction conditions optimization was carried out for the most suitable temperature, solvent, and base system [30].

The complexes of cobalt(III), nickel(II), and copper(II) have been synthesized and reported using an asymmetric bidentate N,O donor Schiff base ligand (HL), where L = 2-[(4-methoxy-2-nitrophenyl)iminomethyl]phenol) [43].

Also, the synthesis and characterization of some series of Cu(II) complexes of Schiff base ligands with ONS donor and triphenylphosphine employing EPR spectroscopy, elemental analysis and IR spectroscopy as characterization techniques have been reported [44]. These complexes were then applied in the catalytic N-arylation of imidazoles using various arylhalides (chlorides and bromides). This was conducted in N,N-dimethyl acetamide solvent at an elevated temperature of about 120 °C, with K_2CO_3 serving as a base. The obtained yields of the products were reported to be appreciable (88-98%) [44].

Furthermore, the synthesis and full characterization of nickel(II) and palladium(II) complexes with novel bis(oxazoline) ligands have been considered of great interest. Considering the relative positions of the oxazoline moieties on the phenyl spacer, they were able to study the coordination behavior of these ligands [5].

The ortho-bis(oxazoline) (G) (Figure 4), facilitates chelate coordination due to the close proximity of the two nitrogen atoms of the oxazolines. However, for the 1,3 and 1,4-bis(oxazoline) ligands (B and C) (Figure 5). On the other hand, only the pincer and bimetallic compounds are formed respectively. Interestingly, C_2 symmetry of the ligand A was lost after co-ordination to the N,N-bidentate points of attachments. This is an important structural feature for this ligand. Therefore, in complexes of the ligand (A), two

similar groups on the metal trans- to each the nitrogen atoms in the complexes were observed to be non-equivalent both in solution and in the solid state. In addition, the isomers can be differentiated from one another by the process of halogen substitution. For example, this can be demonstrated in the formation of metal-bis(oxazoline) complexes G and H [5].

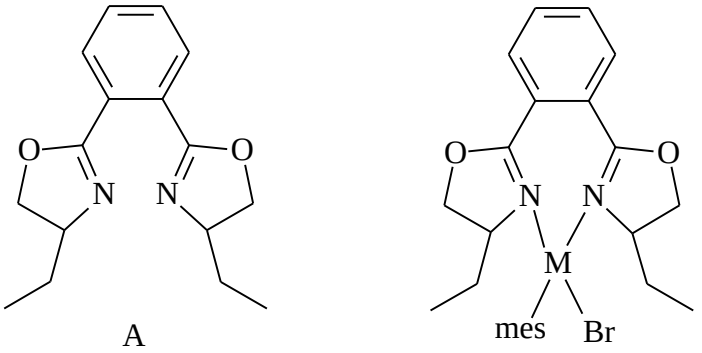
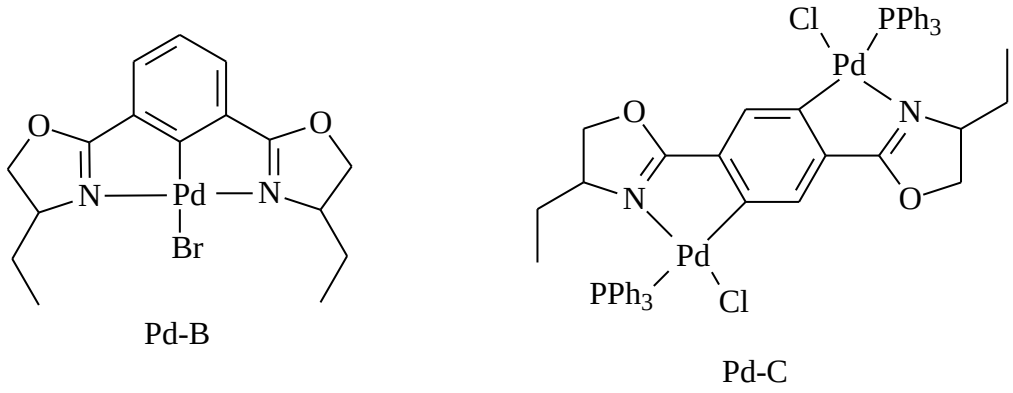


Figure 4: Example of some reported Metal-bis(oxazoline) complexes

The low asymmetric induction in organic transformations observed with ortho-bis(oxazolinyl)aryl ligands could be attributed to this coordination behavior, for example, Cu-catalyzed cyclopropanations [45] or allylic substitutions catalyzed by palladium complex [46]. In the latter case, low enantiomeric excesses are obtained due to their more accessible transition states, as the nucleophile has similar though different energetic positions that could be attacked on the substrate. Furthermore, metallacycles were obtained with ligands (B and C) via cyclopalladation processes. In ligand (C) (Figure 1), two C_{aryl}–H bond activations took place on the phenyl spacer to stabilize the bis-metallated compounds, while for ligand B on the other hand, as a result of selective

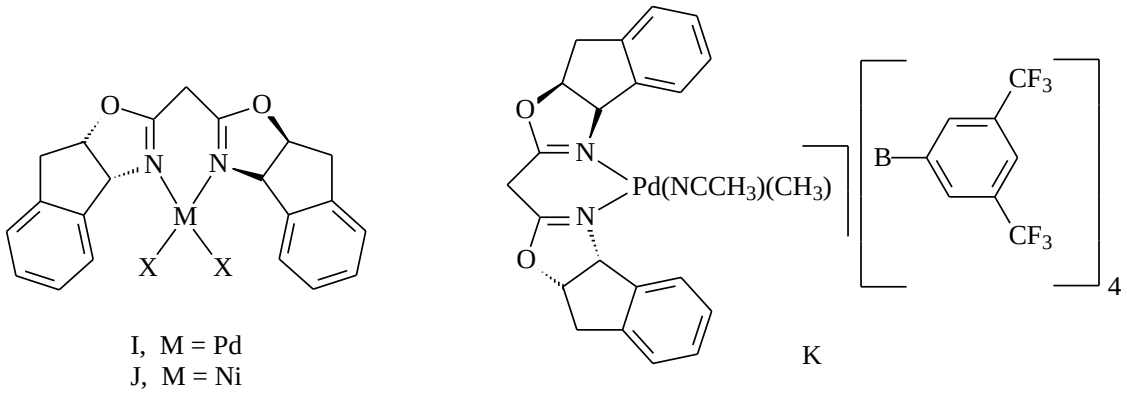
activation of the C_{aryl}–H bond on the phenyl spacer between the two oxazoline substituents, a terdentate complex was obtained (Figure 5) [5].



Pd-B Pd-C

Figure 5: Terdentate and bi-metallic palladium-bis(oxazoline) complexes from ligands B and C

The synthesis of novel chiral dihalido palladium(II) and nickel(II) complexes bearing a bis(oxazoline) ligand ((1R,2S)-inda-box) that is conformationally constrained was described and reported [47]. A monoalkyl complex C, $[Pd(NCCH_3)(CH_3)]B(Ar_f)_4$ (where Ar_f = 3,5-bis(trifluoromethyl)benzene) and dichloridopalladium(II) complex [{(1R,2S)-inda-box}$PdCl_2$] were synthesized. X-Ray structure analysis was employed to determine the solid state structure of the complex A; dichloridopalladium(II)complex [{(1R,2S)-inda-box}$PdCl_2$] [47]. The structures of these complexes are presented below (Figure 6):



I, M = Pd
J, M = Ni

K

Figure 6: Some examples of chiral metal-bis(oxazoline) complexes

Furthermore, the catalytic asymmetric Passerini reaction was carried out employing bidentate coordinating substrates by using tridentate bis(oxazolinyl)pyridine(pybox)-Cu(II) complex [Figure 7], benzoic acid, (benzyloxy)acetaldehyde, and p-methoxyphenyl isocyanides as a way of invoking the stereo-control of the newly formed C-C bond, hence achieving a yield and ee of 98% and 98% respectively [48].

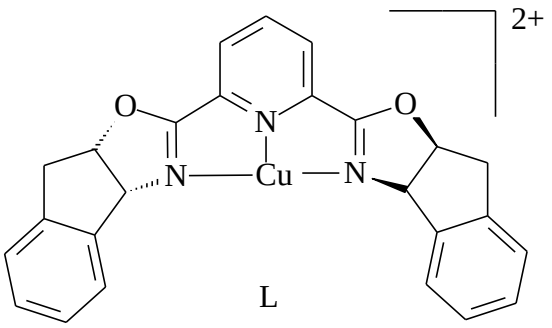


Figure 7: Tridentate Cu(II)-bis(oxazolinyl)pyridine(pybox) complex

In addition, the success in the synthesis and characterization of some novel nickel complexes bearing benzoxazolylpyridines using FTIR spectroscopic and elemental analysis have been disclosed in the literature. In addition, [$NiCl_2${2-(2-benzoxazolyl)-6-methylpyridine}] and [$NiCl_2${2-(5-methyl-2-benzoxazolyl)-6-methylpyridine}] had their molecular structures established using single-crystal X-ray diffraction. The former has two penta-coordinated Ni(II) centers, and is a binuclear centrosymmetric compound. While the latter, which is a mononuclear, was found to have a distorted geometry of octahedral-coordination around the nickel atom. These complexes were observed to be catalytically active in ethylene oligomerization, and giving α-butene selectivity in dimerization of ethylene. The different ligand environments and effects of reaction parameters were the explanations given for the observed variance in the catalytic

activities of the complexes [49]. Also, most recently, the reports of some novel bis(oxazoline) complexes of palladium (Pd-BOX-1, Pd-BOX-2, Pd-BOX-3 and Pd-BOX-4) (Figure 8) synthesized by our research group, having high catalytic activities and recycling abilities for application in coupling reactions have been documented [30,38].

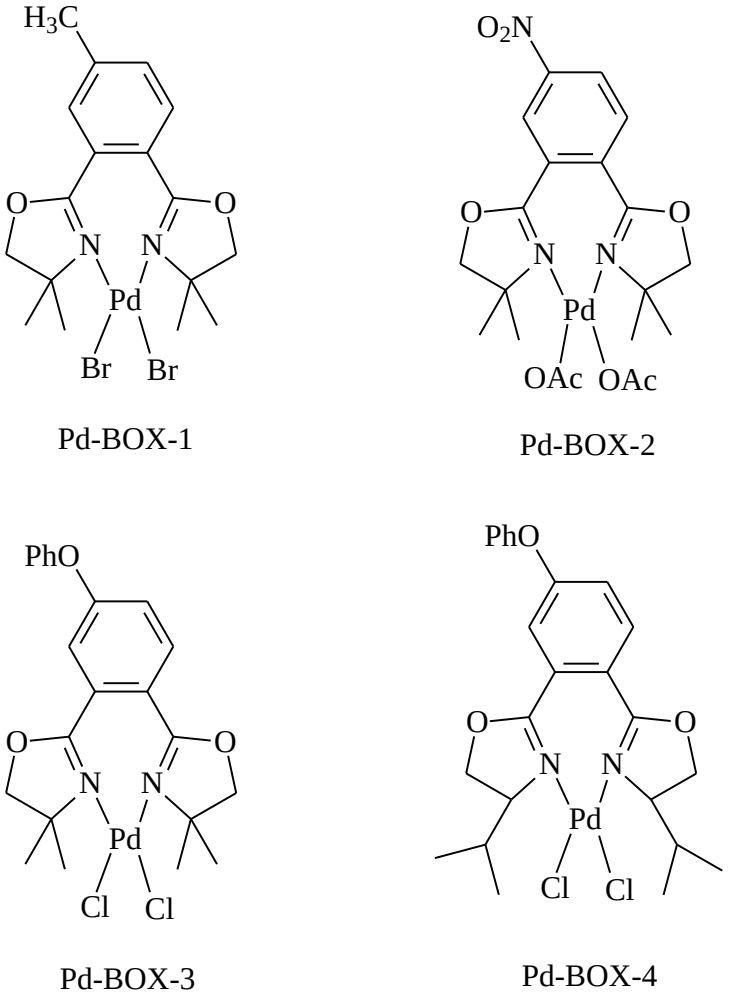


Figure 8: Some recent palladium-bis(oxazoline) complexes

Bis(oxazoline) complexes of copper have been intensively employed in different types of catalytic Diels-Alder reactions. The reactions of 3-propenoyl-2-oxazolidinone with

various substituted dienes were successfully conducted and high enantioselective yields of the products were obtained when [Cu((S,S)-t-Bu-box)]$(SbF_6)_2$ was used in the reaction. Also, analogous Diels-Alder reactions were also successfully catalyzed and adopted in the total synthesis of some important organic molecules [50].

1.4 Cross coupling reactions

Cross-coupling reactions among the different reactions catalyzed by palladium complexes have become very powerful and important route for making new C-C bonds. Generally, less-reactive organic electrophiles (commonly aryl halides) are involved in bond formation with different carbon nucleophiles catalyzed by palladium complexes [51]. In recent years, C-C coupling reaction became indisputably one of the most eminent reactions in organic synthesis. Numerous systems have been designed to carry out such reactions, especially catalytic systems. In 2009, a review on sustainable silica-palladium catalyst systems for cross coupling reactions was conducted and the outcome was reported [52]. They indicated that most novel heterogeneous catalysts are rooted on the basis of silica supports, as silica presents some favorable properties, such as their porous nature and fantastic accessibility, incredible thermal and chemical stability, and most importantly, the support that gives on the surface to robustly anchor organic to provide catalytic centers. These sustainable silica-palladium catalyst systems were among the most extensively used for carbon–carbon and carbon–nitrogen bonds formation [52]. Palladium-catalyzed cross-coupling reactions have been improved considerably since the discoveries of Suzuki, Miyaura, Mizoroki, Heck, Neigishi and other coupling reactions. The reason for their increasing acceptance and popularity is due to the remarkable

characteristics of the strategies and their high tolerance to a wide scope of functional groups on either coupling substrates. Hence, it was possible to successfully create and develop large multi-complex organic building blocks efficiently in much fewer steps relative to the traditional stoichiometric reactions. Also, the development of novel ligands and co-catalysts permits for the amelioration of the reactivity and selectivity. Therefore, it is not surprising that these reactions are commonly used for numerous applications. The significance and distinction of these reactions in modern organic chemistry has resulted in the three major coupling reactions (Heck reaction, Suzuki coupling, and Negishi coupling reaction) being awarded a Joint Nobel Prize in Chemistry in 2010 (Figure 9).

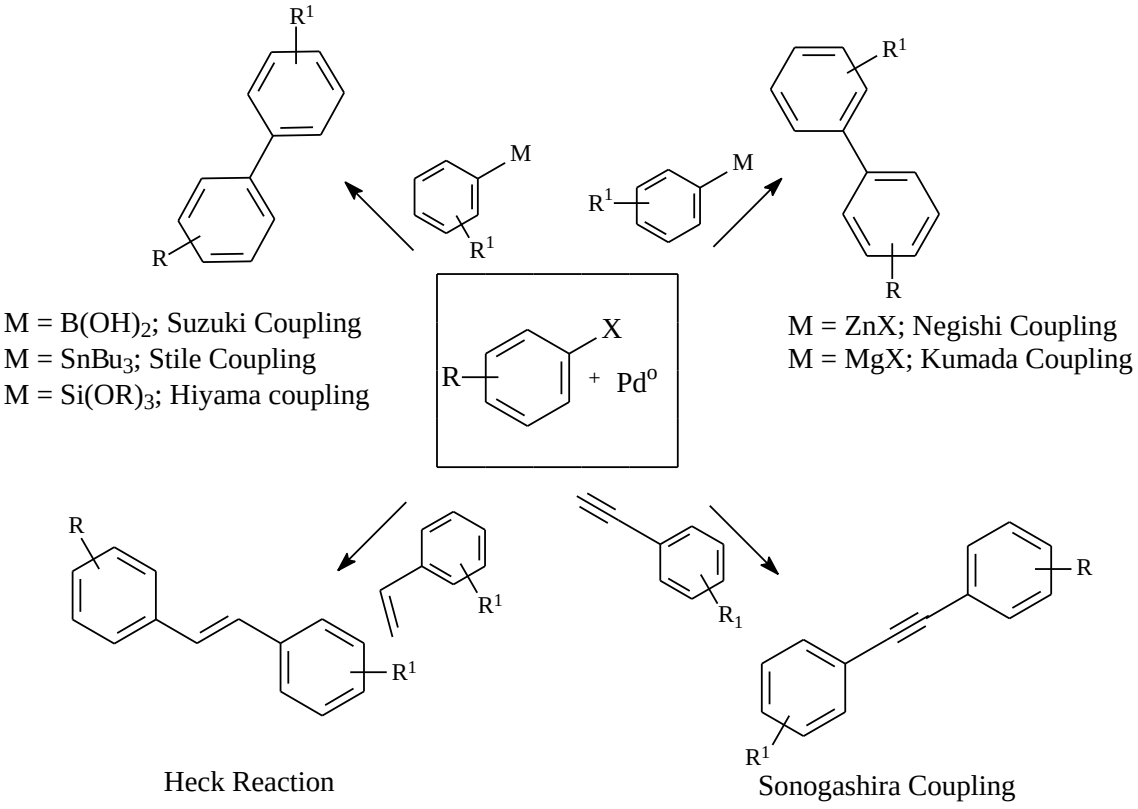


Figure 9: Common palladium catalyzed coupling reactions [51]

1.4.1 Suzuki-Miyaura coupling reactions

This reaction was invented by Akira Suzuki, a Nobel Prize laureate. The reaction is indisputably one of the most substantial synthetic routes for the carbon-carbon coupling of both symmetrical and unsymmetrical biaryls [53]. The majority of reports presented new palladium compounds uses Suzuki–Miyaura coupling of some variety organic halides and organoboron reagents as a guide for testing the catalytic abilities of the metal complexes. However, some people may argue that testing new palladium catalysts in Suzuki reactions is predominantly not regarded to be significant, as it has been already observed, and that even ligand-free palladium salts catalyzed the reaction between aryl bromides and phenylboronic acid substrates in aqueous medium [54]. In addition, this reaction can be catalyzed with even trace concentrations of range 20–50 ppb of palladium found in "ultrapure" sodium carbonate under tolerable conditions at about 150 °C [55-56]. Hence, the results obtained for this reaction using any palladium catalyst must be treated with great care, except where less-reactive substrates like aryl chlorides are used [57]. Over 34% of the catalysts tested for these reactions were reported to catalyze the reaction of aryl chlorides which are less-activate substrates with phenylboronic acid in various optimized reaction conditions in water or other solvent mixtures. The type and nature of the catalyst determines the conditions of reaction such as the reaction temperatures and the reaction time. In 2007, the first report for the full conversion of the reaction of aryl chlorides substrates in Suzuki reaction with the NHC ligand was reported to have been achieved after 12 h of reaction at 100 °C. However, tolylboronic acid was used as coupling reagent instead of the normal phenylboronic acid [58]. The fundamental advantage of Suzuki-Miyaura coupling reaction is the use of air-stable and readily

available aryl boronic acids as the coupling substrate. All these methods have been developed further and are applied today regularly on an industrial scale. Organoboron reagents are used as nucleophiles in Suzuki coupling reactions [59]. These reagents such as boronates and organoboronic acids have the ability to transfer their organic moieties to the palladium center via a base-assisted transmetalation reaction. Aryl boronic acids or borates readily available and/or can be easily synthesized from trialkylborates with a common organometallic compounds like the organolithium or Grignard reagents. For this reason, the Suzuki reaction is still perhaps an important method for the synthesis of all kinds of biaryl derivatives. In addition, they are both moisture and air stable and they have high tolerance to numerous functional groups. They have been also assessed to have a low toxicity. The fact that several biaryls are popular sub-structures in natural products, pharmaceuticals, agrochemicals, and new electronic materials, stands as a reason to explore the application of the Suzuki reaction that should not be limited to only academic research but also extensively employed for the production of fine chemicals even for the industrial production scale [51]. The Suzuki coupling reaction mechanism follows similar mechanistic steps as that of the Negishi coupling reactions (Figure 10). First, it starts with aryl halide been oxidatively added to the palladium(0) center, and then followed by the transmetalation with the organometallic reagent, and finally the reductive elimination of the transmetalated product to yield the product and the regeneration of the active palladium(0) catalyst. Obviously, the main difference between the two coupling reactions lays on the step where the organometallic reagent is relocated i.e. the transmetalation step.

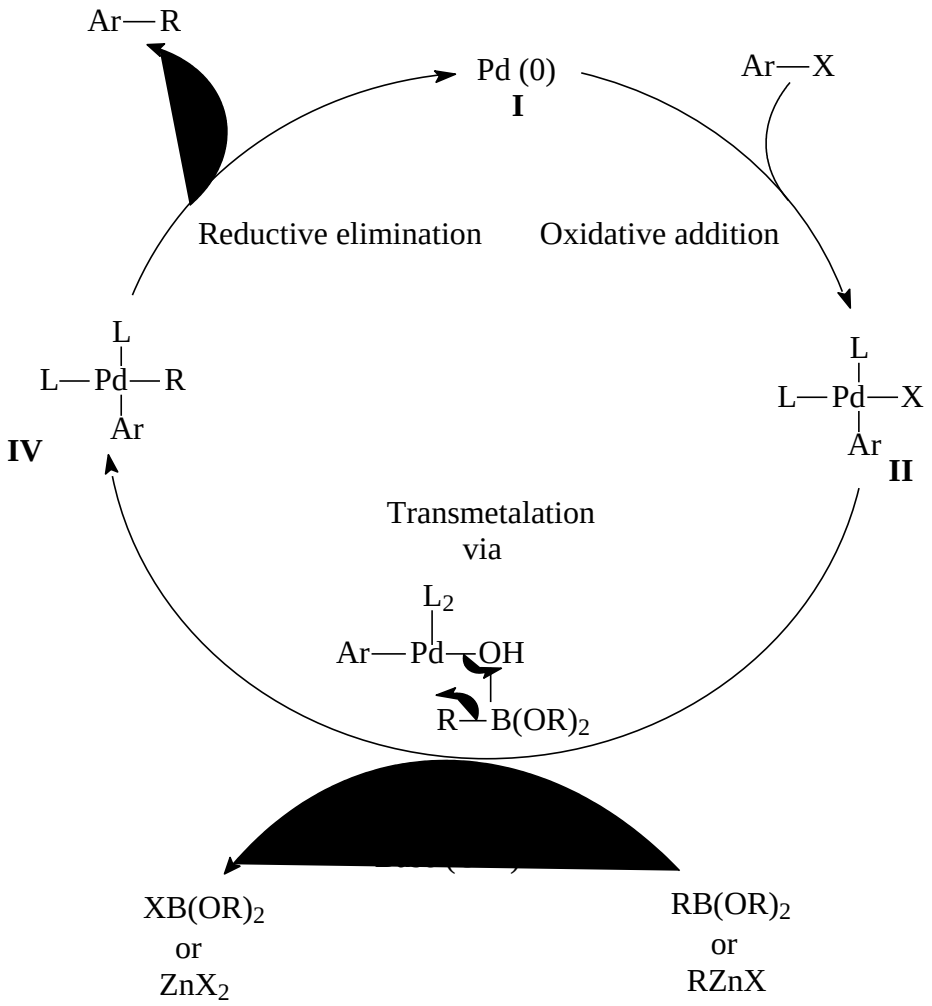


Figure 10: General reaction mechanism for the Negishi and Suzuki cross-coupling reactions [60]

A successful synthesis of a glycopeptide antibiotic called vancomycin was reported using cross-coupling reaction, after several failed attempts. This shows the incredible power of this synthetic approach, as all the biaryl units in the drug were coupled by Suzuki reaction [61].

The Suzuki–Miyaura coupling reaction of aryl halides with aryl boronic acids which are usually more efficiently catalyzed by palladium complexes are a multifaceted method for biaryl synthesis. Various reports showed the formation of biaryls under rigorous reaction

conditions and for a long reaction time. In 2013, in our laboratory, unveiled details on the utilization of a new palladium-bis(oxazoline) complex with an inherent chirality in Suzuki reaction has been reported. High isolated yields (>99%) in DMF, at elevated temperature in the presence of potassium carbonate for 6 h were obtained [30]. Novel palladium bis(oxazoline) catalytic systems were recently developed in our laboratory applied in cross coupling reactions. Sukuzi coupling reaction was optimized to lead to high yields at room temperature reaction and short reaction time (20 minutes) by the reaction of 4-iodoacetophenone and phenylboronic acid. The successful cross-coupling of a wider scope of aryl halides (iodo, bromo and even chloro) with some stream of various boronic acids were achieved. Interestingly, excellent cross coupling products were isolated in excellent yield (93-99%) [62]. In addition, the novel catalyst also exhibited a promising recycling ability investigated in the Suzuki–Miyaura coupling reaction of iodobenzene and p-tolylboronic acid in a mixed DMF/H_2O solvent at a temperature of 70 °C for 1 h, showing a constant catalytic activity without loss of the catalytic activity even after recycling for 12 times. In addition, various coupling reactions leading to biaryls formation carried out at ambient temperature in a short reaction time, employing Pd-BOX-1 in solvent system H_2O/Organic as a novel catalytic system were reported [38]. The reaction was optimized using this catalytic system DMF/H_2O (1:1), K_2CO_3 and room temperature. In order to investigate the consistency and the activity of the novel catalysts, the optimized conditions of the catalytic system were adopted for numerous substrates. Aryl iodide with electron withdrawing substituents like $COCH_3$ and NO_2 and electron donating substituents such as OCH_3 and NH_2 were coupled successfully with various substituted and non-substituted phenylboronic acids giving the respective coupling

products in appreciate yields (>90%). In spite of the activity of this novel catalyst, the nature of substitution on the benzene ring affects the rate reaction. Aryl iodides having electron withdrawing groups reacted more rapidly with full conversions obtained within 20 min. However, aryl iodides with electron releasing substituents took at least 90 min to attain complete conversions. The two aryl halides, aryl bromide and aryl chloride, which are known to be the less reactivate aryl halides in the Suzuki–Miyaura coupling reactions were also considered with phenyl-boronic acid. The reaction of the less reactivate aryl bromides gave yields of 99% in the respective coupling product but at a much prolonged reaction time (12 h), and the least reactive aryl chloride gave traces of products at ambient temperature and high yield (90%) at elevated temperature (110 °C) after 12 h. It was reported in 2010 that Suzuki–Miyaura coupling reactions were carried out successfully at room temperature with high purity of the targeted product and a good yield in neat water using a ([1,1´-biphenyl]-2-yloxy)diisopropyl-phosphine ligand ortho-coordinated to palladium in a cyclic manner. It was fully characterized; the crystal structure was obtained, and was applied to a wide substrate range [63].

1.4.2 Mizoroki-Heck coupling reactions

Palladium chemistry began to make its way into organic synthesis about 5 decades ago. In traditional synthetic organic chemistry, in order to make C-C bond, in pericyclic reactions, it requires stoichiometric reactions of electrophiles with reactive nucleophiles. Nevertheless, unexpectedly, oxidative catalysis gave birth to today's carbon–carbon bond-forming strategy. For example, the oxidative conversion of olefins to carbonyl compounds, such as conversion of ethylene to acetaldehyde employing palladium(II) complex catalyst, known as a Wacker process [64], was believed to be the key to the

inspiration for the exploration of further applications. Perhaps for Richard Heck as well who, in the 1960s, worked with Hercules Corporation as an industrial chemist. He was able to use aryl mercury compounds in the late 1960s to develop numerous coupling reactions using a stoichiometric amount of palladium(II) complex or at least in low catalytic amounts. Accordingly, part of this novel work was published in 1968 in an exceptional series of seven continuous articles [65-71]. He continued his research work and only until in 1972 with the discovery made based on the reaction of phenylmercuric acetate with lithium tetrachloropalladate under a saturated atmosphere of ethylene, generating high yield of styrene (80%) with a minor product, trans-stilbene, in around 10% yield [62]. He illustrated a strategy that was able to discover the coupling of styrene with iodobenzene, emerging as today's popularly known coupling "Heck reaction" [72]. In 1971, Tsutomo Mizoroki had published a very similar reaction [73-74]. However, Mizoroki could not make it to see the good part of the story on the reaction, and died of cancer at his early age. In the Mizoroki–Heck reaction or simply Heck reaction, the halides of (hetero) aryl, alkenyl, and benzyl were reacted with various kinds of alkenes with the help of palladium catalysts to give the respective substituted alkenes (Scheme 4) [75-77]. The reaction typically progresses with high regio- and stereoselectivity. After significant improvements observed in the 1980s and 1990s, this synthetic approach was availed tremendously from this valuable reaction (Heck reaction), especially that it can easily be applied for the synthesis of important pharmaceuticals, agrochemicals and many more complex organic compounds [51]. Heck reactions became one of most important palladium catalyzed reactions. It has a reactivity nature based on the palladium-driven catalytic cycle, which occurs from the ability of palladium(0) species to allow varieties of

several C-X bonds to be added oxidatively forming RPdX intermediates to unsaturated bonds. In fact, Heck chemistry is related with the catalytic arylation and alkenylation of olefins. The most general acceptable mechanism for Heck reaction starts with the oxidative addition of R-X (where R is any substituted or unsubstituted aryl, and X could be any of the halides I, Br, Cl, or other anions e.g. OTf, OTs, $N\equiv N\text{-}BF_4$, C=O(Cl), SO_2Cl etc.) to an activated palladium(0) center, forming the corresponding palladium(II) species (Figure 11) Subsequently, the alkene is coordinated and then inserted on this palladium(II) center generating an alkylpalladium complex. β-H elimination of this alkylpalladium complex takes place after carbon–carbon bond rotation to satisfy the conditions for β-H elimination, releasing the substituted alkene as the product and regenerating the active palladium(0) specie and a base. This cycle is repeated continuously until all the reactants have completely reacted.

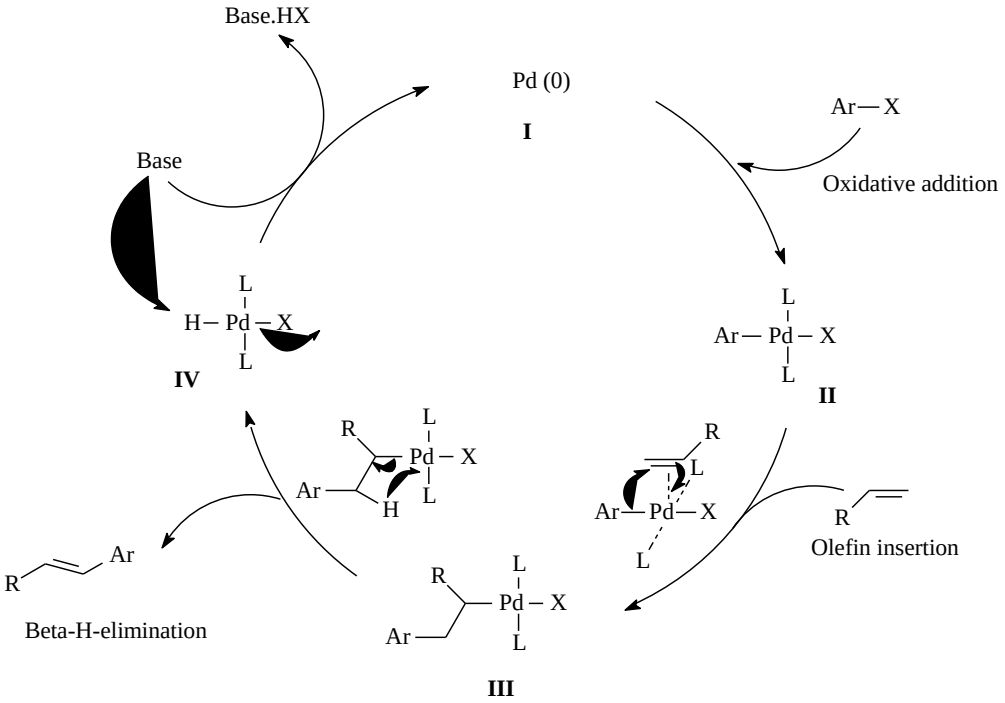


Figure 11: General reaction mechanism for the Heck reaction [78]

Akeel S. Saiyed reported a Mizoroki–Heck coupling reaction applying aminooxazolines as potential ligands for the synthesis of stilbene and its derivatives [79].

In our laboratory, Mizoroki–Heck coupling reactions were also carried out at 70 °C with substituted olefins and various aryl iodide substrates, catalyzed by a palladium-bis(oxazoline) (Pd-BOX-3) (Figure 12) complex with an inherent chirality. Excellent isolated yields were obtained (95-97%) for all the substrates employed under the reaction conditions for 12 h, except for the reaction of iodobenzene and styrene, which gave an isolated yield of 65%. This yield was improved to 92% at 110 °C [30]. Some palladium-bis(oxazoline) complexes (Pd-BOX-1, Pd-BOX-2, Pd-BOX-4) were screened for the Mizoroki–Heck coupling reactions of styrene and iodobenzene. All complexes gave excellent yields (99%, 97% and 96%) respectively, in a mixture of DMF/H_2O (3:1) as a solvent system and in the presence of KOH. Palladium-bis(oxazoline) complexes were much more effective as compared to the various palladium commercial complexes and are readily available of 2,2´-bipyridine and 1,10-phenanthroline bidentate nitrogen donor ligands (Figure 8) tested under the similar reaction conditions [38].

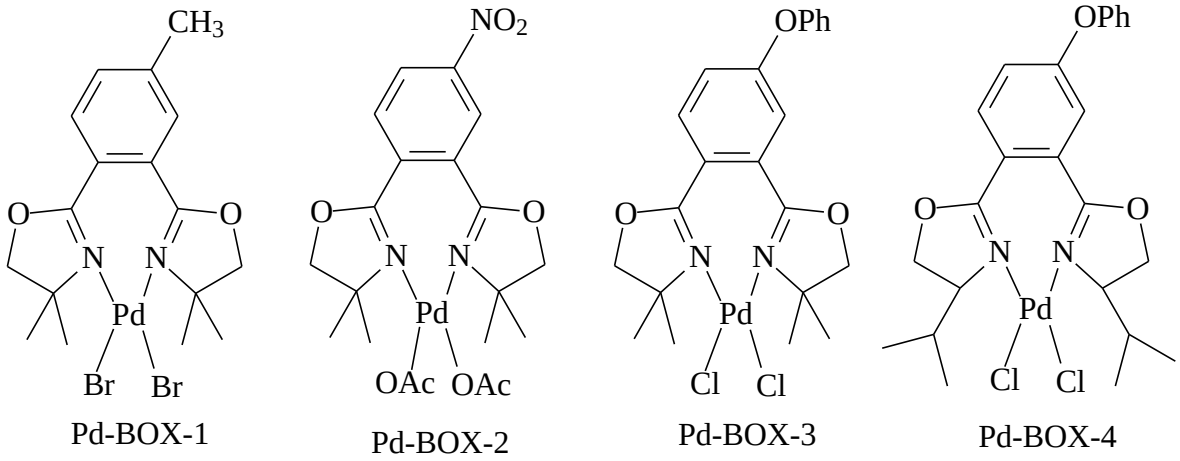


Figure 12: Palladium bis(oxazoline) complexes employed in Heck reaction [38]

1.4.3 Sonogashira coupling reactions

Sonogashira was among the pioneers of this reaction in attempt to develop a better approach for the Stephans-Castro coupling of both aryl iodides [80] and iodoalkenes [81] with copper(I) arylacetylenes. Other scientists have worked in parallel on the same idea such as Heck [82] and Cassar [83]. Sonogashira reported the catalytic substitution reaction of acetylene hydrogen under mild reaction conditions with aryl halides and aryl alkenes, specifically, iodoarenes, bromoalkenes and bromopyridines by using cuprous iodide as a co- catalyst and bis(triphenylphosphine)palladium dichloride as the catalyst in diethylamine. Diphenylacetylene was obtained through recrystallization from ethanol as the major product (85%). Other coupling products were obtained in appreciable yields by following the same procedure. Sonogashira was able to propose a mechanism for the reaction by suggesting that bis(triphenylphosphine)dialkynyl palladium(II) was first formed, which reductively eliminates 1,4-diphenylbutadyne to give a palladium(0) specie, bis(triphenylphosphine)palladium(0). Aryl or vinyl halides subsequently added oxidatively to the palladium(0) specie, accompanied by alkynylation of this adduct to produce an aryl or vinyl derivative of the palladium(0) specie. The reductive elimination gives the substituted product, while the palladium catalyst is regenerated [84]. Tang-Ing Ho et al. reported a method to reduce the undesirable acetylene coupling by-products and promote the targeted cross-coupling products under a reduced atmospheric conditions in order to remove any available oxygen, and hence preventing the oxidation of Pd(0) to Pd(II), which favors homo-coupling products. Consequently, several donor substituent carrying terminal arylethyne, diarylethyne and a small number of new arylpyridylethynes have been obtained in an excellent amount [85]. Many types of internal and terminal

alkynes have been synthesized employing Sonogashira coupling under mild conditions. In fact, most of the reactions can be accomplished under ambient temperature condition [86]. Two new non-C2- symmetric palladium-bis(oxazoline) complexes (Pd-BOX-3 and Pd-BOX-4) were screened for Sonogashira coupling reaction of iodobenzene with phenylacetylene. Isolated yields of 75% and 52% were reported for the complexes Pd-BOX-3 and Pd-BOX-4 respectively, with CuI as a co-catalyst and in the presence of an organic base (Et_3N), at 70 °C [30].

Sonogashira coupling reactions normally were carried out in mixed solvent systems, usually organic/aqueous. The reactions in neat water depend on the solubility of the substrates and catalyst employed, and this makes it highly uncommon [87]. The reactions of aryl bromides are relatively less effective than that of aryl iodides, and aryl chlorides are even much more demanding substrates [88]. The reactivity of the halide and the selection of the particular ligand for the Sonogashira coupling reaction determine the extent of the harshness to be imposed on the reaction [89]. In 2008, a novel approach for coupling aryl bromides with terminal acetylenes at ambient temperature conditions in neat water and in the absence of copper was reported [90].

In Sonogashira reaction, the palladium(0) active precursor plays a vital role in the catalytic cycle of the reaction. In fact, it controls reactivity and structure of both palladium(0) and alkylpalladium(II) complexes involved in oxidative addition [91], in general, it was adopted that the catalytic cycle follows the typical steps of a palladium-catalyzed cross-coupling starting with oxidative addition [92-93], through transmetalation [94-95] and finally reductive elimination [96-97], after which the catalyst is regenerated. The first publication on this work, reported by Sonogashira, suggested a similar catalytic

cycle [96]. For copper free Sonogashira reactions, there are even fewer mechanistic suggestions in the literature. Two mechanistic pathways seem feasible, though their description is not yet fully clarified. They have in common the initial oxidative addition of the RX (aryl halide) and then the subsequent coordination of the alkyne. However, while one of the mechanisms involves the subsequent deprotonation and finally reductive elimination as the last stage, the other is completed by consecutive carbopalladation and subsequent hydride elimination [77, 98-99]. Below are the two mechanisms (a) proposed by Soheili et al. [100] and (b) Heck et al. [99], respectively (Figure 14). Carbopalladation mechanism as proposed by Heck was depicted hypothetically in the catalytic cycle.

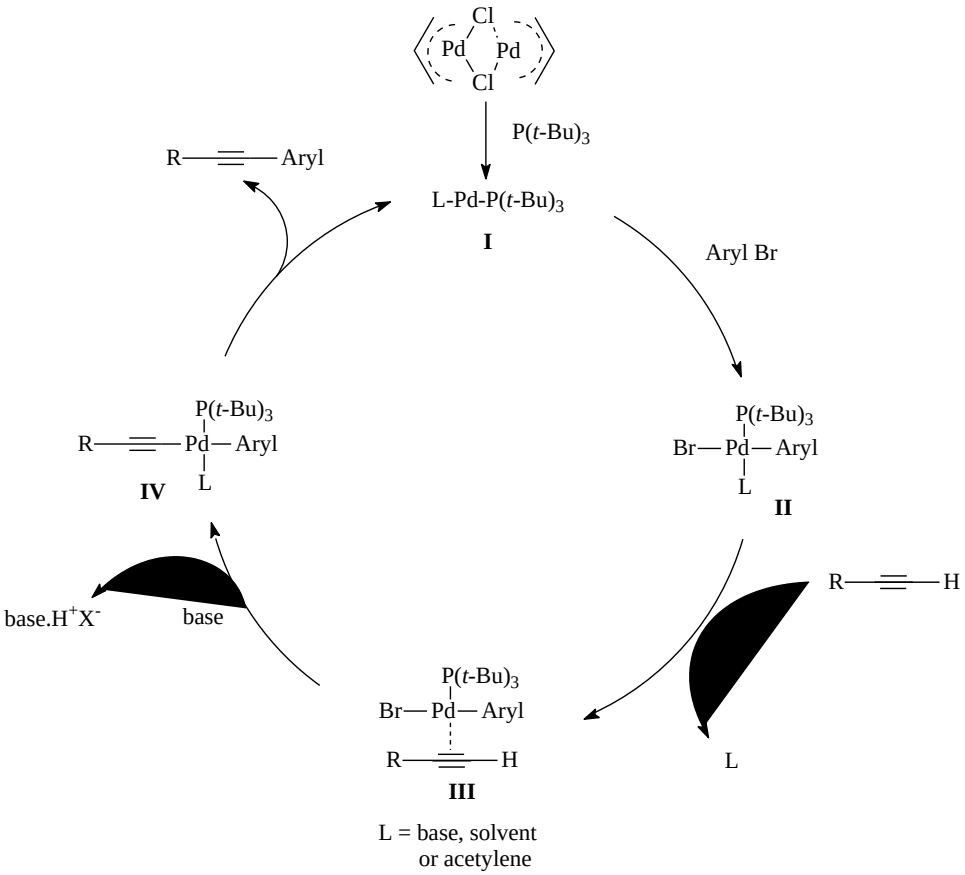


Figure 13: Catalytic cycle of copper free Sonogashira reaction proposed by Soheili et al [100]

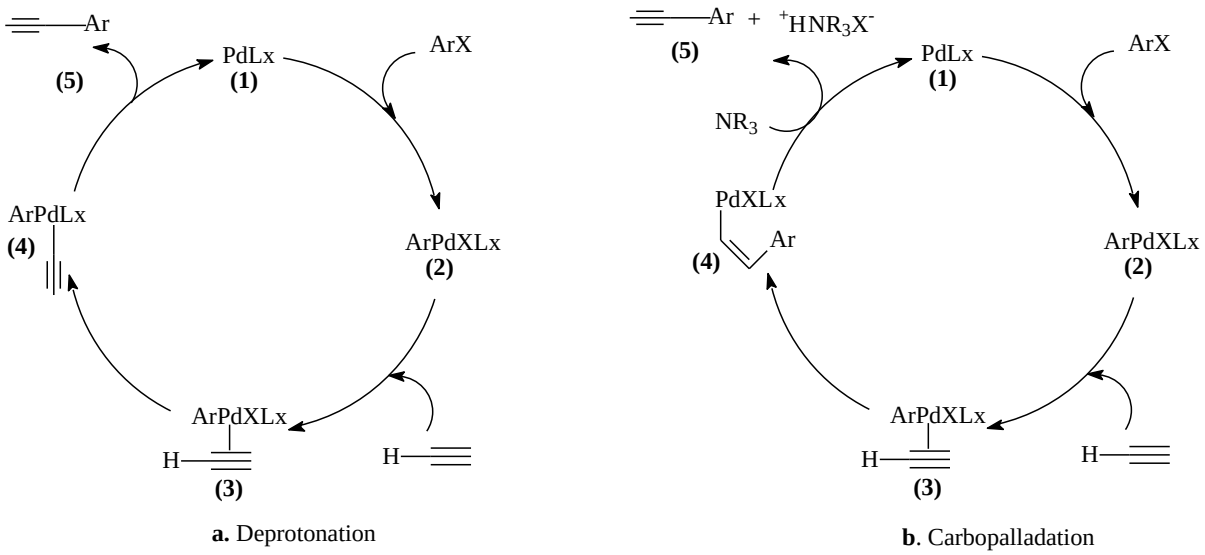


Figure 14: Comparison between the two mechanisms for palladium-catalyzed copper-free cross-coupling between a terminal alkyne and an aryl halide as proposed by (a) Soheili [100] and (b) Heck [99]

1.5 C-H arylation of arenes

The enormous impact made by palladium-catalyzed cross-coupling in the field of chemistry with several applications in the production of complex natural product, in drug discovery and in manufacturing of many useful materials, has been recognized by honoring these scientists with the chemistry Nobel Laureate Prize in 2010. In the past decades, more research was focused on the improvement of late transition metals compounds for catalytic applications, especially in coupling reactions. Recently, C-H activation has received high attention mainly due to some important characteristics related to the diversity and tunable features of the catalysts and their robustness. The valuable late transition metal catalysts, commonly palladium, ruthenium, rhenium and iridium catalysts have been ascertained to be highly promising for catalytic coupling reactions and have been attested to play important roles in facilitating C-H activation efficiently. Nevertheless, their applications were limited due to their low natural

abundance, relatively high level of toxicity and somewhat high cost. Since then, the chemistry of organonickel has received a significant attention for similar applications. Nickel can similarly undergo many of the same elementary reactions as other group members. It is an abundant transition metal that is characterized with a d^{10} configuration and can exist in a wide range of oxidation states, ranging from (0)–(IV), the most common are the lower oxidation states (0) and (II), while the Ni(I) and higher oxidation states [i.e. Ni(III) and Ni(IV)] are rather infrequent. Nickel undergoes quite a number of reactions, it readily loses electrons. Hence, oxidative addition is a common reaction [101]. This is not surprising as nickel is an intrinsic late transition metal of comparable electropositivity. However, nickel can barely undergo reductive elimination as it is much more demanding reaction [102]. Considering the fact that oxidative addition is the primary initiating step in transition-metal-catalyzed cross coupling reactions, the facile oxidative nature of nickel permits the use of electrophiles such as phenol derivatives [103], aromatic nitriles [104] and even aryl fluorides [105], which would have reasonably lower activity under the palladium catalyzed conditions. Most palladium catalyzed reactions revolve around palladium oxidation states of (0) and (II) in their catalytic cycles, and usually proceeds via well-known mechanisms. Similarly, Ni(0) and Ni(II) oxidation state are very common in the catalytic cycles of nickel catalyzed reactions. In addition, the states (I) and (III) in nickel are easily accessible, leading to different possible mechanisms and reactivity. Therefore, the transformations with nickel catalysts with oxidation states ranged (0) to (III) are common. In fact, there are catalytic cycles where nickel is retained as Ni(I) oxidation state [106]. For these similarities, nickel based complexes have often been exclusively considered as the best substitute for cross-

coupling reactions catalysts due to the cost efficiency as compared to palladium. Despite the fact that these metals display enormous potential in the direct C–H bond functionalization due to their low price and specific reactivity profiles, the nickel is relatively not properly utilized. During the past several years, an increasing number of nickel catalyzed C–H functionalization has been reported in the literature. Diverse nickel catalyzed reactions have revealed the common misconception about nickel compounds. Indeed, homogeneous nickel catalysis is presently at the peak of intensive research exploration [107].

1.5.1 C-H arylation of unactivated arenes

The wide scope of significant coupling reactions has been highly explored due to their importance in obtaining arenes or biaryl based pharmacophores and other highly functional group compatibilities. Although several challenges were encountered in linking natural products and other complex organic molecules due to their large ratio of C_{sp3}-C_{sp3} to arene-carbon linkages found in these compounds. Efforts have been made to achieve a systematic route for the stereospecific aliphatic formation of C-C bond in a similar way to biaryl or aryl-heteroatom bond formation were revolutionized via the breakthrough in cross coupling. A practical direct C–H arylation of unactivated arenes and C–H arylation of pyridine with aryl halides using a nickel catalyst under relatively mild conditions and without the use of any additive was reported [39], suggesting its potential for developing an efficient and practical applications route. $Ni(OAc)_2 \cdot 4H_2O$ in the presences of 1,10-phenanthroline ligand and KOtBu as a base were used as the catalyst system (Figure 15). This provides a catalyst system, based on nickel, that is

relatively cheap and readily available and therefore presents an added value to the direct C–H arylation of arenes.

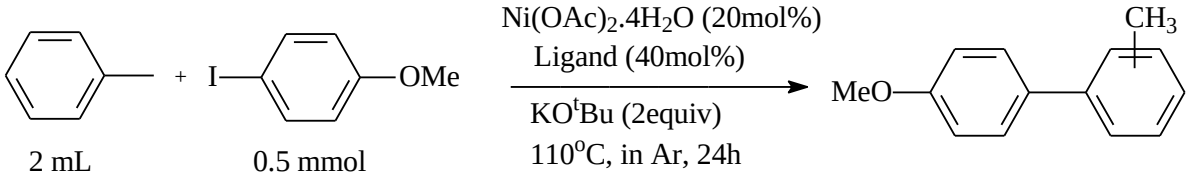


Figure 15: C-H arylation of toluene with 4-iodoanisole

Various ligands were investigated for this reaction. The three active ligands that gave appreciable conversion were 1, 10-phenonthroline and its derivatives, labeled as M, N and O, which gave conversions of 55%, 54% and 51%, respectively (Figure 16).

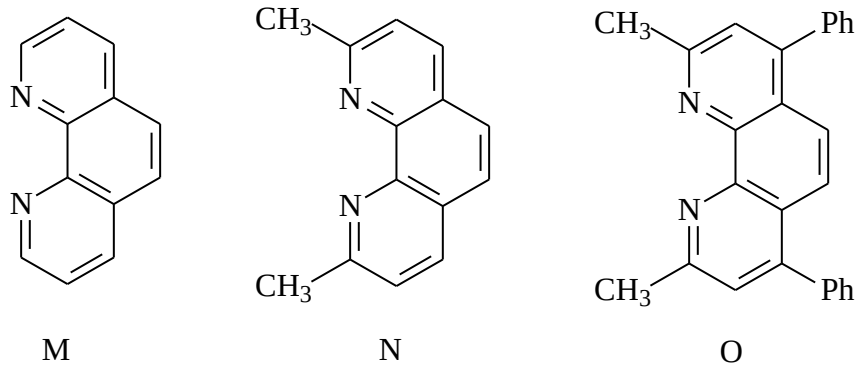


Figure 16: Some of the 1,10-phenonthroline and derivatives ligands used for the C-H arylation reaction

Also, various Aryl iodides were tested using high base amount (4 equiv.) with benzene in place of toluene in the presence of the ligand A and relatively good yields were obtained [39]. Nickel(II) dicyclopentadiene and triphenylphosphine have been utilized as the catalytic system for the direct heteroarylation of excess pyridine (62 equiv.) using a strong base such as t-BuOK and an aryl bromide as the coupling partner. The mixed positional isomers (2, 3, and 4-arylpyridine) were obtained as products, where 2-

arylpyridine appeared to be the major product in all cases, and total yields ranging from 53-73% were obtained [108].

1.5.2 C-H bond functionalization

The reactions that lead to the formation of carbon–carbon bonds are among the most vital processes in the field of organic chemistry because they provide the principal steps in building up of highly complex molecules from low simple precursors that are readily available. It has always been the dream of synthetic organic chemists to develop an environmentally friendly synthetic tool that could be used in this area. In the last decade, a green nickel-catalyzed functionalization of C–H bonds for assembling new C-C bonds has emerged. One of the key merits of C-H activation, for example, for the direct functionalization of a hydrocarbon, unlike the common cross-coupling, halogen pre-functionalized substrate is not required. For example, the synthesis of an important complex organic molecule called muscoride A by itami et al [109], describing an uncommon route of arylation of benzoxazoles and benzothiazoles via nickel catalyzed C-H activation in the presence of an electrophilic coupling partner, usually aryl esters, giving the desired (hetero)biaryl coupling product. The method has now been adopted formally for the synthesis of this molecule as it gives an excellent yield. An effective $NiCl_2$-catalyzed single pot coupling of aldehydes and amines in the presence of a terminal alkyne was developed by Samai et al. giving different propargylamines as products with high yields (up to 95%) [110]. The reaction is very effective and a green process as the only by-product from this reaction is water. Hence, it unambiguously has very high atom efficiency. Accordingly, a mechanistic breakdown of the reaction has been proposed to probably follow a sequence of steps involving the activation of the C–H

bond of alkyne by the catalyst ($NiCl_2$) giving a nickel–acetylide intermediate which further react with the iminium ion, which is produced in situ from aldehyde and amine generating the corresponding propargylamine.

1.6 Carbonylative coupling reactions

De Lassone in the 18th century discovered carbon monoxide (CO) gas after heating zinc oxide with coke. Later, W. C. Cruikshank worked on similar reaction and was the first to identify this gas [111]. Today, CO is used as a readily available and cost effective C1-source for carbonylation reactions as it has a very high atom economy. Transition metal-catalyzed carbonylation was first carried out at the beginning of the 20^{th} century. Since then, a magnificent progress has been attained in this research area. Notably, in addition to academic developments, carbonylation reactions with CO were applied in the industry on a large scale. For example, carbonylation of methanol is used for the industrial production of acetic acid (Monsanto or Cativa process) [112]. Other examples of industrially established carbonylation processes are summarized on (Table 1).

Heck and his coworkers were first to report palladium-catalyzed carbonylation in the 1970s [113-114]. They were able to demonstrate the reaction of vinyl and aryl halides with carbon monoxide leading to acylpalladium intermediates which subsequently react with various appropriate nucleophilic substrates to yield carboxylic acids, esters, aldehydes or amides. Coupling of organic nucleophiles or/and electrophiles are required in the oxidative carbonylation reactions catalyzed by palladium catalyst, under pressurized CO condition and an oxidant afforded for the synthesis of various carbonyl-containing compounds (Figure 17). Various transition metals catalyzed reactions have been used in the manufacturing process of several compounds, which serve as important

intermediates in the production of dyes, pharmaceuticals, agrochemicals, and other industrial products such as ketones, esters, amides, α-keto amides, ureas, oxamates, carbamates, oxamides, oxazolidinones etc. Nowadays, a number of transition metal catalysts are readily available [115].

A state-of-the-art method for the synthesis of acid chloride through the efficient carbonylation of aryl iodide catalyzed by palladium complex was illustrated. The complex readily eliminates the acid chloride reductively from the intermediate palladium-Aroyl complex that has a sterically demanding phosphine ligand (P^tBu_3) and coordinated CO ligand, which assists in fast and efficient carbonylation process [116]. The convertibility of acid chlorides ranked them among the most commonly used building blocks in synthetic organic chemistry. The acid chlorides have found wide applications in so many synthetic routes, covering the synthesis of simple esters and amides, the peptide coupling [117], the industrial polymerization [118], the Friedel-Craft acylation [119], and the metal catalyzed carbon-carbon bond formation [120]. They are employed as acylating agents even with weakly active nucleophiles due to their highly electrophilic nature. In spite of that, the most challenging problem with the acid chlorides is how they can be produced. Several approaches have been attempted; the typical one is from the reaction of an organic acid and a chlorinated reagent usually PCl_3 or thionyl oxalyl chloride. These chlorinated reagents are highly reactive species that need to be generated first. Moreover, these species are high energy ones, hence they lead to a pronounced chemical waste. In addition, they are hazardous; PCl_3 and thionyl chloride are under schedule 3 of the Chemical Weapon Convention guidelines. Therefore, there was an increased challenge to develop a more reliable approach. The palladium catalyzed carbonylation of aryl halides

was one of the most promising approaches for the production of acid chlorides. β-lactones, which are important components of many natural products (e.g. valilactone [121], malyngolide [122] etc.), have been prepared via carbonylation of epoxides. This approach was essential because epoxides have been classified as highly reactive, cheap and readily available substrates [123]. Similarly, the carbonylation of aziridines by ring expansion lead to the synthesis of β-lactams, which are very important intermediates in pharmaceutical industries [124]. Various C-glycoside as natural products have shown promising medicinal significance with potentials for treating fungal and tumorigenic infections [125]. Several important biologically active compounds have been synthesized through carbonylation reactions. For example, the synthesis of C-glucoside 8, 10-di-O-methylbergenin, which constitute several synthetic steps, had one key step that involves the palladium(0)-catalyzed aryl carbonylation [126].

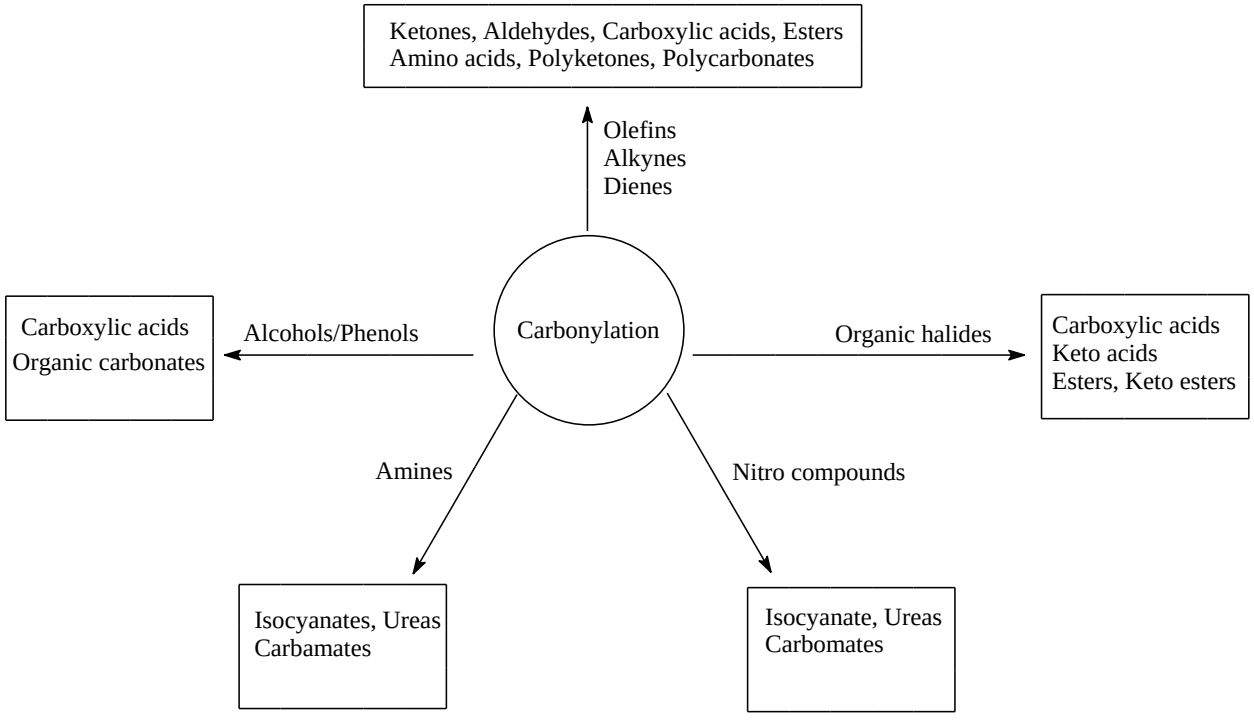


Figure 17: Scope of carbonylative coupling reactions

Recently, various research studies have focused more on various aspects of the carbonylation reactions including the separation of catalyst from the product and strategies of recovering and reusing catalysts. For this reason, emphases have been laid on the improvement of anchoring homogeneous catalysts by employing a number of techniques including supported liquid phase catalysis and biphasic catalysis. Carbonylation strategies employing these approaches are elegant, economical, and highly effective, and giving desired products in excellent yields. The air/moisture sensitivity of phosphine ligands, in addition to high costs and tedious work-up procedures, discourages their use in this process and make the overall process economically unfavorable. Various carbonylation processes carried out under phosphine-free conditions provided highly economical and elegant strategies for these transformations and, hence, these paths eliminate the use of toxic non-air stable phosphine ligands [105].

Alkoxycarbonylation, aminocarbonylation, double carbonylation and oxidative carbonylation are the major types of carbonylation reactions that have received considerable attention in the last decades. However, the most common carbonylation reactions are alkoxycarbonylation and aminocarbonylation. These reactions represent efficient approaches for the synthesis of esters and amides under palladium-catalyzed catalytic system using aryl halides and alkynes as substrates. Several palladium-catalyzed homogeneous and heterogeneous catalytic strategies have been established for the synthesis of these precious products [118, 127-128]. Carbonylation reactions have been applied in several industrial processes that produce around 8 million tons of products. The table below shows the carbonylation processes, the catalyst employed for each process and the company known for the commercialization of the process.

Table 1: Industrial carbonylation processes

Process	Catalyst	Company
Methanol to acetic acid	$Co_2(CO)_8$	BASF
	$[Rh(CO)I_2]^-$	Monsanto
	$IrCl_3$-$RuCl_3$	BP
Acetylene to acrylic acid	$NiBr_2$-$CuBr_2$	BASF
Ethylene to propionic acid	$Ni(OCOC_3H_5)_2$	BASF
Butadiene to adipic acid	$HCo(CO)_4$	BASF
Isobutylphenyl ethanol to Ibuprofen	$PdCl_2(PPh_3)_2$	Hoechst Celanese
Propylene to methyl Methacrylate	Pd-pyridyl Phosphine	Shell
Ethylene copolymerization to polyketones	$Pd(OAc)_2$/dppp, TsOH	Shell

The research area that is presently receiving highly considerable attention in synthetic organic chemistry is the involvement of small molecules for the development of novel processes [129-130]. Metal-catalyzed carbonylation is an important process in synthetic chemistry that is widely applied in industry for the synthesis of carbonyl compounds due to the ease of accessibility of such compounds [131]. However, the carbonylation reactions requires CO gas, which has some unavoidable drawbacks associated with its use, particularly regarding safety and other related issues [118,132]. Considering the great significance of carbonylation reactions for pharmaceutical and industrial applications [118], there is a need for simplistic reactive alternate carbonyl synthons to

allow these processes to be carried out safely. For this reason, other carbonyl sources have alternatively been explored as carbonyl synthons in place of gaseous CO for numerous synthetic transformations, examples are formates, formamides, chloroform, aldehydes, and metal carbonyls [119]. Various triarylbismuth and triarylindium have been converted to ketones and esters under palladium catalyzed conditions in carbonylation reactions using oxalyl chloride as CO source as reported by Maddali L. N. Rao et al [133]. Surprisingly, the production of ketones via carbonylative coupling of CO gas with triarylbismuths was found to be ineffective using the same catalytic system, under the same conditions [134]. Tibor Gracza recently reported a more efficient CO generation protocol via Zn-mediated reduction of the oxalyl chloride used as a novel reaction system for Pd-catalyzed carbonylation of aryl halides. This readily available CO source substitute can efficiently generate in situ CO. In addition, carbon monoxide generated outside the reaction system has been employed successfully in a newly designed two-chamber system for a number of Pd-catalyzed carbonylative reactions under mild conditions of reaction. The use of oxalyl chloride for carbonylation reactions makes it easily feasible and more efficient [135]. In general, carbonylation reactions that adopt the use of reagents that generate CO in situ are very safe.

1.6.1 Alkoxycarbonylation of aryl halides

One of the most regarded synthetic organic chemistry transformations is the conversion of aryl halides to carboxylic acid esters. Conventionally, the synthesis of carboxylic acids goes through halogen-metal exchange by alkyllithium or Grignard reagents, followed by the addition of carbon dioxide. However, a more effective and convenient approach for the synthesis of carboxylic acids and their esters is the use of palladium-catalyzed

carbonylation of aryl halides, under CO gas, in the presence of an appropriate alcohol. This strategy has found wide range of applications especially in the preparation of different esters [136-137]. An immobilized palladium metal containing ionic liquid was used as the heterogeneous catalytic system for alkoxycarbonylation reactions of various iodobenzene derivatives and different types of alcohols [138]. The catalyst was able to be recycled with excellent yields up to four times consecutively. Palladium/carbon has been also employed by several research groups for the alkoxycarbonylation of aryl halides. Liu et al. used Pd/C to develop an efficient, versatile and recyclable protocol for these reactions [139]. Salvadori et al. used a micro dielectric heating condition using Pd/C to carry out the alkoxycarbonylation of various alcohols including aliphatic aliyclic, chiral alcohol and phenols with aryl halides to produce excellent yields of products and two recycling runs of the catalyst [140]. Manabe et al. demonstrated the use of N-formylsaccharin and phenyl formate as a source of CO in palladium catalyzed reductive carbonylation of aryl halides [141]. Paraformaldehyde, as a source of carbon monoxide, has been considered for alkoxycarbonylation to avoid the toxicity of CO gas, which many synthetic organic chemists consider a disadvantage. Consequently, various aryl bromides have been converted successfully to desirable aromatic aldehydes and esters with appreciable yields [142]. Palladium catalyzed alkoxycarbonylation of methanol and 4-bromoanisole in the presence of a phosphine ligand smoothly produced the corresponding methyl ester in 85% isolated yield [143]. 4-Methoxycarboxylic acid was also produced in high yield (94%) in the same way using water in place of methanol after small modification of the conditions described in the literature [144].

1.6.2 Aminocarbonylation of aryl halides

Aminocarbonylation was reported to have been achieved at room temperature and low CO pressure, with a catalytic amount of $Pd_2dba_3 \cdot CHCl_3$, in acetonitrile, using ethyldiisopropylamine as an organic base, in the presence of an appropriate amine, iodobenzene and a tertiary butyl ammonium chloride (Bu_4NCl). A yield of 92% was obtained with the best screened ligand (P^tBu_3). Other ligands, however, gave poor yields of the products [106]. The use of polymer supported catalyst was reported to give excellent yields of products with high selectivity in the carbonylation of both aromatic and aliphatic amines with aromatic and heteraromatic halides [145]. Dang et al. demonstrated the use of palladium nanoparticles supported on zeolitic imidazole framework (ZIF-8) in the aminocarbonylation of various aryl halides. This catalytic system has some advantages which include the large surface area, high water and air stability and tolerance to high temperature even in acid, base or alcohols [146]. In a similar way to alkoxycarbonylation, the immobilized palladium metal in ionic liquid was used as heterogeneous catalytic system for aminocarbonylation reactions of various iodobenzene derivative and different amine types [124]. Since 1860, CO was known to be generated via chloroform hydrolysis in the presence of a strong base [147]. Various primary and secondary amines were used in palladium-catalyzed aminocarbonylation reactions of aryl, vinyl and benzyl halides, with the CO generated rapidly and in high yields from the hydrolysis of chloroform in the presence of $CsOH.H_2O$. The yield of the amide as a carbonylation product was high (91%) with DPEPhos when 3 equivalents of $CsOH.H_2O$ was used [148]. This approach is really interesting as it considers cheap and commercially available bulk chemicals. More interestingly, the isotopically labeled forms

$^{13}CHCl_3$ and $^{14}CHCl_3$ are also available commercially, thereby giving a room for easy facile incorporation of isotopically labeled CO into organic and organometallic compounds yielding products that are enriched isotopically. $Pd(PPh_3)_4$ catalyzed the aminocarbonylation of various aryl bromides with benzylamine in dioxane, using NEt_3 as a base at 95 °C [149]. The carbonylation reaction realized using $(COCl)_2$ as the CO gas source (2 equivalent of CO for every 1 mole of $(COCl)_2$) using Zn powder provided the corresponding benzyl amides in appreciable yields [122].

1.7 Research problem identification

Homogeneous catalysis has the advantage that metal coordination sphere can be modulated to achieve high activity and high selectivity. There are a good number of publications that describe the synthesis and catalytic applications of palladium and nickel complexes and other metal complexes having phosphine and nitrogen based ligands in homogeneous catalysis including the cross-coupling and C-H activation reactions. However, the phosphine ligands and their metal complexes are highly air and moisture sensitive and relatively toxic. While on the other hand, the reports describing the synthesis and applications of active palladium and nickel having nitrogen based ligands in coupling reactions and C-H activation reactions are very few.

Carbon-carbon coupling reactions and C-H activation are extensively explored research areas in synthetic organic chemistry. Palladium complexes have been considered widely for cross- coupling reactions [28] and nickel complexes have been used in arylation reactions under mild conditions [29]. The method of C-H activation by nickel complexes

is highly attractive due to the advantages of the nickel to be readily available and cheaper than the palladium counterpart.

The current research is focused on the design and development of new bis(hydroxymethyloxazoline) ligands and their nickel and palladium complexes and the investigation of their catalytic applications in cross-coupling reactions, direct C-H arylation reactions and carbonylative coupling reactions. These complexes are attractive due to their air and moisture stability and to their high catalytic activity at relatively mid reaction conditions. The new bis(hydroxymethyloxazoline) ligands are unique due to the presence of the hydroxyl groups, which should improve the catalytic activity of the corresponding metal complexes in water as their solubility in aqueous medium is improved.

1.8 Aims and objectives

The aims and objectives of this research project are:

1. Synthesis and characterization of novel bis(oxazoline) ligands carrying hydroxymethyl groups.
2. Synthesis and characterization of novel palladium(II) and nickel(II)bis(hydroxymethyloxazoline) complexes.
3. Evaluation of the catalytic performance of the palladium(II) bis(hydroxymethyloxazoline) complexes in Suzuki-Miyaura, Mizoroki-Heck and Sonogoshira coupling reactions.
4. Evaluation of the catalytic performance of the nickel(II) bis(hydroxymethyloxazoline) complexes in direct C-H arylation reactions of arenes.
5. Evaluation of the catalytic performance of the palladium(II) bis(hydroxymethyloxazoline) complexes in alkoxycarbonylation and aminocarbonylation of aryl halides.

CHAPTER 2

BIS(OXAZOLINE) LIGANDS, NICKEL AND PALLADIUM BIS(OXAZOLINE) COMPLEXES: SYNTHESIS AND CHARACTERIZATION

2.1 Introduction

The synthetic approach for the bis(oxazolines) (BOX) of interest in this work is analogous to that described by L. Mei et al. [150]. The synthesis and characterization of nickel(II) and palladium(II) complexes formed with bis(oxazoline) ligands were reported [5]. Accordingly, they were able to study the coordination behavior of the nitrogen atoms of the BOX to the metal centers using various ligands and also by changing the relative positions of the oxazoline moieties on the phenyl group [5]. There are several reports for bis(oxazoline) ligands with C_2-symmetry and their complexes with various transition metal ions in the literature [151]. Nevertheless, the reports that link to non-chiral bis(oxazoline) ligands of nickel and palladium are very scanty [152]. In the current chapter, we present the synthesis and characterization of two new bis(oxazoline) (BOX-OH) and two oxazoline (OX) ligands and the corresponding Pd(II)-BOX-OH, Pd(II)-Pyr-(OX-OH), and Nickel(II) BOX-OH-1 and Copper(II) BOX-OH-1 complexes. The X-ray crystal structure of Pd-BOX-OH-1 complex is also represented.

2.2 Experimental and methodology

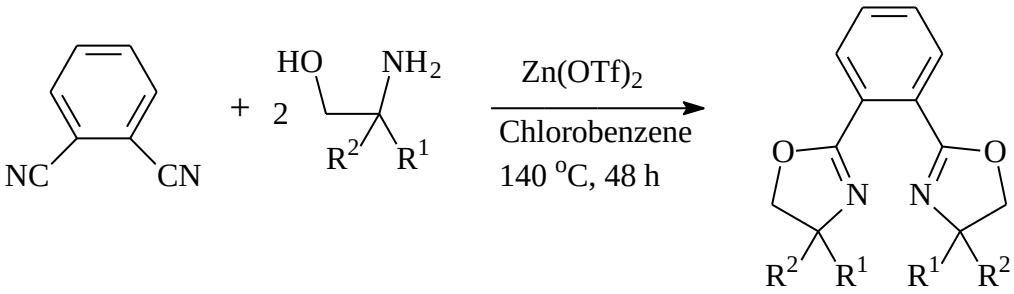
All the chemicals and materials employed throughout the synthesis of both the bis(oxazoline) ligands and the palladium and nickel complexes were in high purity as they were all used as purchased from the respective chemical companies. All the solvents employed for the synthesis were in their anhydrous forms or freshly distilled. The products obtained were all purified employing flash column chromatography, packed with 60F Silica gel purchased from Fluka Chemie AG (Buchs, Switzerland) and, hence, all products were obtained in their purest forms.

500 MHz NMR machine (Joel 1500 model) was used to carry out all the NMR analysis, obtaining the ^{1}H and ^{13}C NMR spectral data. Tetramethyl silane (TMS) was employed as reference and the chemical shifts were recorded in ppm and $CDCl_3$, DMSO-d_6 and D_2O as solvents. IR spectra (cm^{-1}) were recorded with (Perkin-Elmer 16F model) FTIR spectrometer. Elemental analyses were conducted using a Perkin Elmer Series 11 (CHNS/O) Analyzer 2400. TLC plates supported by silica gel obtained from Sigma Aldrich (250 µm layer thickness) were adopted for thin-layer chromatography analyses. A Varian Saturn 2000 GC-MS machine was used to analyze the products.

2.2.1 General procedure for the synthesis of bis(oxazoline)

The mixture of phthalonitrile or its derivative (4.0 mmol) and zinc triflate (0.20 mmol) in dried chlorobenzene (30 mL) were stirred at ambient temperature for about 15 minutes. A solution of the appropriate aminoalcohol (8.0 mmol) in dried chlorobenzene (5 mL) was added slowly. The reaction mixture was set to run under reflux at a temperature of about 135 -140 °C for about 24 hours. The reaction was monitored using TLC throughout the

reaction time, until the intensity of the starting spot was relatively unchanged over a period of at least 3 hours. The excess chlorobenzene was removed by rotary evaporation method. The reaction product was then dissolved in 30 mL of ethyl acetate:methanol (1:1) and then extracted twice with distilled water (2 x 20.0 mL). The organic and aqueous layers were then separated using a separating funnel, and the combined organic phases were dried using anhydrous sodium sulfate. The ethyl acetate / methanol solvent mixture was removed using a rotary evaporator to obtain the crude product, which was then purified employing the appropriate solvent system (ethyl acetate:methanol) as eluent in silica gel column chromatography [150].



R^1 =CH_2OH, R^2 = CH_2CH_3, (BOX-OH-1)
R^1 =CH_2OH, R^2 = CH_2OH, (BOX-OH-2)

Figure 18: Synthesis of bis(oxazoline) (BOX-OH-1 and BOX-OH-2)

2.2.2 General procedure for the synthesis of oxazolinyl benzoic acid (OX-COOH)

Phthalic acid (1.2 mmol) and amino phenol (3.6 mmol) were added into a preheated 50 mL polyphosphoric acid (85% phosphorus pentoxide) placed in a two necked 200 mL round bottom flask. The mixture was then refluxed by heating to 140 °C for 24 h. The

reaction mixture was poured immediately onto cold ice water, covered and left overnight. Afterwards, the reaction mixture was filtered to collect the precipitate which was then washed with a solution of dilute sodium carbonate to neutralize the excess acid and subsequently with pure water to wash the sodium carbonate completely. The precipitate was air dried and purified by employing the appropriate eluent solvent system (ethyl acetate:ether) in silica gel column chromatography to give the pure product.

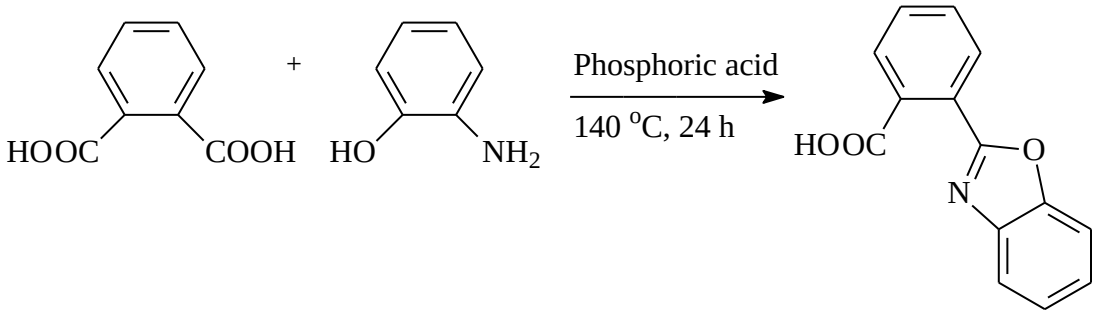


Figure 19: Synthesis of oxazolinyl benzoic acid ligands (OX-COOH)

2.2.2 General procedure for the synthesis of oxazolinylpyridine (Pyr-OX-OH)

A mixture of 4-nitro-2-pyridinecarbonitrile (4.0 mmol) and zinc triflate (0.20 mmol) in dried chlorobenzene (30 mL) were stirred under ambient temperature for 15 minutes. A solution of the appropriate amino alcohol (4.0 mmol) in dried chlorobenzene (5 mL) was then added slowly. The reaction mixture was refluxed at a temperature 140 °C for 24 h. The reaction was monitored using TLC throughout the reaction time, until the intensity of the starting spot was relatively unchanged over a period of at least 3 hours. The excess of chlorobenzene was removed by rotary evaporation method. The reaction product was then dissolved in 30 mL of ethyl acetate:methanol (1:1) and then extracted twice with

distilled water (2 x 20 mL). The organic and aqueous layers were then separated using separating funnel, and the combined organic phase was dried using anhydrous sodium sulfate. The ethyl acetate/methanol solvent mixture was removed using a rotary evaporator to obtain the crude product, which was then purified employing the appropriate solvent system (ethyl acetate:methanol) as eluent in silica gel column chromatography.

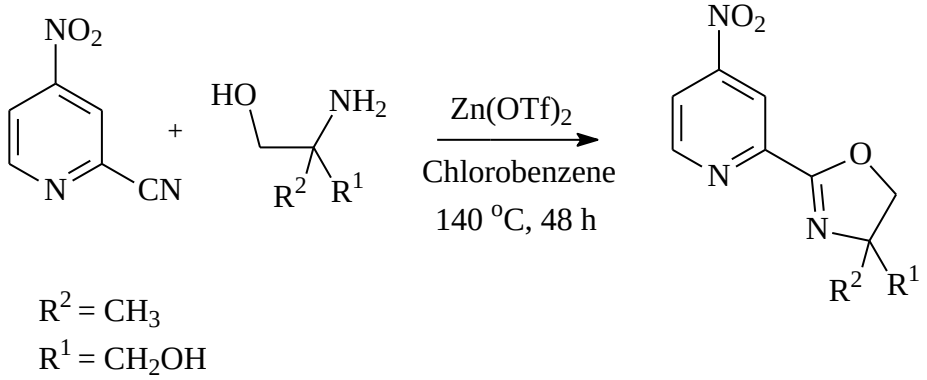


Figure 20: Synthesis of oxazolinylpyridine (Pyr-OX-OH)

2.2.4 General procedure for the synthesis of palladium bis(hydroxymethyloxazoline) complexes (Pd-BOX-OH-1 and Pd-BOX-OH-2)

The below general procedure was adopted for the synthesis of the palladium bis(hydroxymethyloxazoline) complexes: Pd-BOX-OH-1 and Pd-BOX-OH-2 (Figure 21).

Palladium(II) chloride (0.50 mmol), dissolved in DMF (8 mL), and the BOX-OH ligand (BOX-OH-1 or BOX-OH-2) (0.50 mmol) were charged into round bottom 25 mL flask flushed with nitrogen for 15 minutes. The reaction mixture was stirred at ambient temperature for 6 h, while the progress of the reaction was monitored using TLC at 4 h

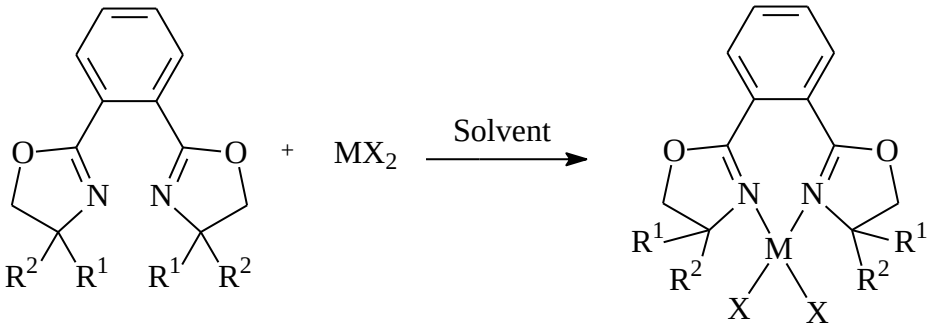
intervals until no significant difference between the intensity of two consecutively spots of the starting material (BOX-OH-1 or BOX-OH-2 ligands) coming from the reaction mixture was observed. The excess reaction solvent was removed using rotary evaporation method. The crude product was then dissolved in DMF and set for slow evaporation to obtain good crystals. These were isolated, washed with dichloromethane and ethanol and then characterized with the various characterization techniques including single crystal X-ray crystallography, ^{1}H and ^{13}C NMR, FTIR spectroscopy and elemental analysis [47, 153-154].

2.2.5 General procedure for the synthesis of nickel(II) bis(oxazoline) complexes (Ni-BOX-OH-1 and Ni-BOX-A)

The following general procedure was adopted for the synthesis of nickel-BOX complexes: Ni-BOX-OH-1 and Ni-BOX-A (Figure 21).

Nickel(II) perchlorate hexahydrate [$Ni(ClO_4)_2.6H_2O$] (1.0 mmol) and BOX-OH-1(1.0 mmol) ligand, nickel(II) acetate [$Ni(OAc)_2.4H_2O$] (1.0 mmol) and BOX-A (1.0 mmol) ligand (1.0 mmol) respectively were dissolved in 10 mL of pure and dry solvent (CH_2Cl_2 or CH_3CN). The reaction mixture was stirred at ambient temperature for 12 h. The reaction was monitored using TLC at 4 h intervals until no significant difference between the intensity of two consecutively spots of the starting material (BOX-OH-1 or BOX-A) was observed. Then, the nickel complex was filtered and washed with dichloromethane. The clear green residue was dried under reduced pressure. The product was washed again with dichloromethane and ether, and the light green solid was then dried to give the pure

product. Several attempts of recrystallization in various solvent systems were made; however, did not afford crystals.



R^1 =CH_2OH, R^2 = CH_2CH_3, M = Pd, X = Cl, (Pd-BOX-OH-1)
R^1 =CH_2OH, R^2 = CH_2OH, M = Pd, X = Cl, (Pd-BOX-OH-2)
R^1 =CH_2OH, R^2 = CH_3, M = Ni, X = ClO_4, (Ni-BOX-OH-1)
R^1 =CH_3, R^2 = CH_3, M = Ni, X = OAc, (Ni-BOX-A)

Figure 21: Synthesis of metal-bis(oxazoline) complexes

2.2.6 General procedure for the synthesis of palladium-oxazolinylpyridine complex [Pd-Pyr-(OX-OH)]

The following general procedure was employed for the synthesis of palladium-oxazolinylpyridine complex Pd-Pyr-(OX-OH) (Figure 22).

Palladium(II) chloride (0.50 mmol) and Pyr-OX-OH (0.50 mmol) were dissolved in DMF (8 mL) and charged into round bottom 25-mL flask flushed with nitrogen for 15 minutes. The reaction mixture was stirred at ambient temperature for 6 h, while the progress of the reaction was monitored using TLC at 4 h intervals until no significant difference between the intensity of two consecutively spots of the starting material (Pyr-OX-OH ligand) coming from the reaction mixture was observed. The excess reaction solvent was

removed using rotary evaporation method. These were isolated, washed with dichloromethane and ethanol and then characterized with the various characterization techniques including ^{1}H and ^{13}C NMR, FTIR spectroscopy and elemental analysis [47, 153-154]. The obtained product was then dissolved in in various solvent systems, including DMF and left for slow evaporation to recrystallize. However, no crystals were afforded.

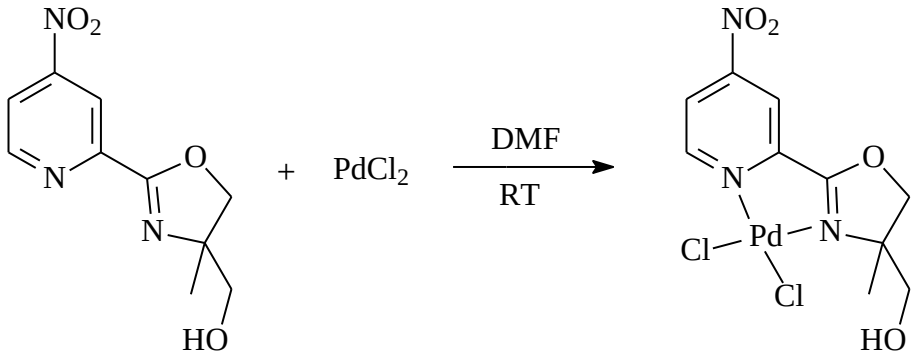
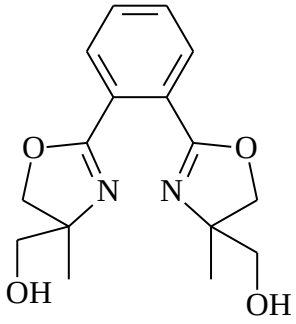


Figure 22: Synthesis of chlorido-4-nitro-2-(4-hydroxymethyl-4-methyl)-2- oxazolinylpyridine palladium(II) [Pd-Pyr-(OX-OH)] complex

2.3 Results

2.3.1 Characterizations of bis(hydroxymethyloxazolines) (BOX-OH) compounds

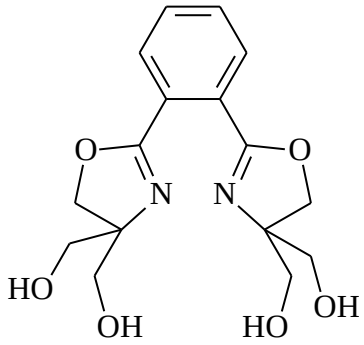
2.3.1.1 [1,2-bis(4-hydroxymethyl-4-methyl-2-oxazolinyl)benzene] (BOX-OH-1)



BOX-OH-1

White solid; isolated yield (93%); ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.66 (dd, ^{3}J = 5.4 Hz, ^{4}J = 3.0 Hz 2H, C*H*-3, 6 arom), 7.56 (dd, ^{3}J = 5.4 Hz, ^{4}J = 3.0, 2H, C*H*-4, 5 arom), 4.79 (td, ^{2}J = 18.3 Hz, ^{4}J = 5.5 Hz 2H, O-C*H*$_2$-4 oxazoline), 4.31 (d, ^{2}J = 7.9 Hz 2H, C*H*$_2$-4 oxazoline), 3.90 (d, ^{3}J = 2H, C*H*$_2$-OH), 3.40 (d, 2H, C*H*$_2$-OH), 1.22 (s, 6H 2CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 161.88 (C, *N=C-O, 2-C-oxazoline*), 161.81 (C, *N=C-O, 2-C-oxazoline*), 130.46 (C-3 *arom*), 130.41 (C-6 *arom*), 129.55 (C-4,5 *arom* x 2) 128.32 (C-*1 arom*), 128.24 (C-2 *arom*), 74.91 (OCH$_2$, *5-C-oxazoline*), 74.84 (OCH$_2$, *5-C-oxazoline*), 72.56 (*CH$_2$OH* x 2) 67.21 [NC(CH$_3$), *4-C-oxazoline* x 2*]*, 23.19 (*CH$_3$*), 23.14 (*CH$_3$*); FTIR (*cm^{-1}):* 3370, 1661, 1085, 1050; GC-MS m/z 305 (M^{+1}); Anal. Calc. for $C_{16}H_{20}N_2O_2$ (304.35): C, 63.14; H, 6.62; N, 9.20. Found: C, 62.55; H, 7.60; N, 8.92.

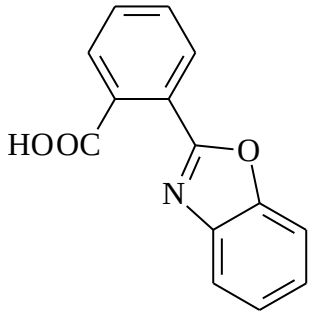
2.3.1.2 [1,2-bis(4,4-dihydroxymethyl-2-oxazolinyl)benzene] (BOX-OH-2)



BOX-OH-2

Pale yellow crystalline solid; isolated yield (82%); ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.70 (dd, ^{3}J = 5.8 Hz, ^{4}J = 3.7 Hz, 2H, C*H*-4,5 arom), 7.58 (dd, ^{3}J = 5.8 Hz, ^{4}J = 3.7 Hz, 2H, C*H*-3,6 arom), 4.68 (dd, ^{2}J = 5.8 Hz, ^{4}J = 5.5 Hz, 4H, O-CH_2-4 oxazoline), 4.24 (s, 4H, *OH*), 3.48 (ddd, ^{2}J = 11.2. Hz, ^{4}J = 10.9 Hz, ^{4}J = 6.4 Hz, 8H, CH_2-OH); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 162.74 (C, *2-C-oxazoline* x2), 130.50 (C, *1,2-CH arom*), 129.68 (C, *3,6-C- arom*), 128.13 (C, *4,5-C-arom*) 77.47 (C, *5-C- oxazoline*), 71.07 (C, *4-C-oxazoline*), 64.02 (C, HO-CH_2 x 4); FTIR (*cm^{-1})* 3401, 1665, 1051; GC-MS m/z 336 (M^{+1}); Anal. Calc. for $C_{16}H_{20}N_2O_6$ (336.34): C, 57.14; H, 5.99; N, 8.33. Found: C, 57.21; H, 4.62; N, 7.57.

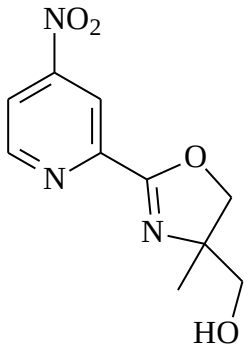
2.3.1.3 *o*-(2-Benzo-2-oxazolinyl)benzoic acid (OX-COOH)



OX-COOH

Brown solid; isolated yield (48%); ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 10.21 (s, *COOH*), 7.87 (m, 4H, C*H* arom.), 7.29 (dd, ^{3}J = 7.8 Hz, ^{3}J = 7.7 Hz, H, *5-benzo-oxazolinyl*), 7.18 (d, ^{3}J = 7.9 Hz, H, *7-benzo-oxazolinyl*), 6.94 (d, ^{3}J = 8.2 Hz, H, *4-benzo-oxazolinyl*) 6.92-6.89 (dd, ^{2}J = 7.5 Hz, ^{4}J = 7.4 Hz, H, *6-benzo-oxazolinyl*); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 167.58 *(COOH)*, 153.60 (*OC=N*), 134.88 (*H, arom*), 131.50 (*H, arom*), 130.69 (*H, arom*), 130.31 (*H, arom*), 123.45 (*H, arom*), 119.53 (*H, arom*), 119.53 (*H, arom*), 116.40 (*H, arom*); FTIR (*cm^{-1}):* 3380, 1702, 1497, 1390, 1100, 1085; GC-MS: m/z 239 (M^{+1}); Anal. Calc. for $C_{14}H_9NO_3$ (239.23): C, 70.29; H, 3.79; N, 5.85. Found: C, 70.12; H, 3.53; N, 5.42.

2.3.1.4 4-Nitro-2-(4-hydroxymethyl-4-methyl)-2-oxazolinylpyridine (Pyr-OX-OH)



Pyr-OX-OH

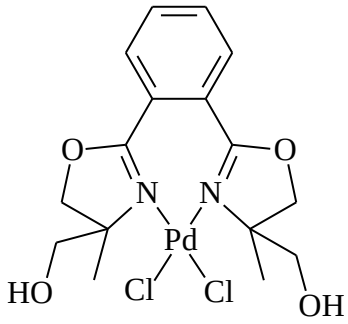
Colorless sticky oil; isolated yield (76%); ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 8.96 (d, ^{3}J = 5.2 Hz, H, 6-Pyr), 8.63 (s, H, 3-Pyr), 8.12 (dd, ^{3}J = 2.1 Hz, ^{4}J = 5.2 Hz, H, 5-Pyr), 4.67 (d, ^{2}J = 8.2 Hz, H, *5-oxazolinyl*), 4.24 (d, ^{2}J = 8.3 Hz, H, *5-oxazolinyl*), 3.86 (d, ^{2}J = 11.6 Hz, H, *4-hydroxymethyl-oxazolinyl*), 3.57(d, ^{2}J = 11.8 Hz, H, *6-hydroxymethyl-oxazolinyl*), 1.40 (s, 3H, *4-methyl-oxazolinyl*). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 161.29 *(N=CO)*, 154.17 (*C, 6-Pyr*), 151.94 (*C, 2-Pry*), 149.06 (*C, 4-Pyr*), 117.93 (*C, 3-Pyr*), 116.62 (*C, 5-Pyr*), 75.72 (*C, 5-Oxazolinyl*), 72.84 (*CH_2OH*), 67.86 (*C, 4-Oxazolinyl*), 23.38 (*CH_3*); IR (*cm^{-1})* 3279, 1630, 1622, 1580, 1072, 1039; GC-MS: m/z 239 (M^{+1}) Anal. Calc. for $C_{10}H_{11}N_3O_4$, (237.22): C, 50.63; H, 4.67; N, 17.71. Found: C, 50.70; H, 4.60; N, 17.62.

2.3.2 Characterizations of palladium(II) bis(hydroxymethyloxazoline) complexes (Pd-BOX-OH)

The characterization of the palladium(II)-BOX-OH complexes was carried out using NMR (^{1}H and ^{13}C), FTIR, EA and X-ray crystallography. The complexes Pd-(BOX-OH)-

1, Pd-(BOX-OH)-2, Pd-OX-Pyr-OH were fully characterized. Although, we were able to establish the crystal structure of only one of these complexes, Pd-(BOX-OH)-1, the other complexes were fully characterized using all the above mentioned techniques, except X-ray crystallography. Below are the characterization details of each of these complexes.

2.3.2.1 [1,2-bis(4-hydroxymethyl-4-methyl-2-oxazolinyl)benzene]chlorido palladium(II) [Pd-(BOX-OH)-1]



Pd-(BOX-OH)-1

Yellow solid; isolated yield (90 %); ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 8.00 (m, H, C*H*- arom), 7.94 (m, H, C*H*-arom), 7.82 (m, 2H, C*H*-arom), 4.72 (d, ^{2}J = 8.3 Hz, H, O-C*H*$_2$-4 oxazoline), 4.68 (d, ^{2}J = 8.9 Hz H, C*H*$_2$-4 oxazoline), 4.33 (d, ^{2}J = 8.8 Hz H, O-C*H*$_2$-4 oxazoline), 4.20 (d, ^{2}J = 8.3 Hz, H, O-C*H*$_2$-4 oxazoline), 3.78 (d, ^{2}J = 11.3 Hz, H, C*H*$_2$-OH), 3.73 (d, ^{2}J = 13.8 Hz, H, C*H*$_2$-OH), 3.49 (d, ^{2}J = 11.3 Hz, H, C*H*$_2$-OH), 3.43 (d, ^{2}J = 11.3 Hz, H, C*H*$_2$-OH), 1.65 (s, 3H, CH_3), 1.49 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 165.60 (C, *N=C-O,2-C-oxazoline*), 164.00 (C, *N=C-O, 2-C-oxazoline*), 133.25 (C-3 *arom*), 132.66 (C-6 *arom*), 130.01 (C-4,5 *arom*), 129.51 (C-4,5 *arom*), 126.77 (C-*1 arom*), 124.91 (C-2 *arom*), 77.69 (OCH_2, *5-CH$_2$-oxazoline*), 76.65 (OCH_2, *5-CH$_2$-oxazoline*), 74.50 (*CH$_2$OH*), 74.15 (*CH$_2$OH*), 66.58 (NC(CH_3), *4-C-*

oxazoline), 65.89 (NC(CH_3), *4-C-oxazoline),* 22.20 (*CH_3*), 20.23 (*CH_3*); IR (*cm^{-1})* 3485, 1646, 1065, 1029; Anal. Calc. for $C_{16}H_{20}$ $Cl_2N_2O_4Pd$ (481.67): C, 39.90; H, 4.19; N, 5.82. Found: C, 40.04; H, 4.13; N, 5.88.

2.3.2.2 The Crystal structure of [1,2-bis(4-hydroxymethyl-4-methyl-2-oxazolinyl)benzene]chloride palladium(II) [Pd-(BOX-OH)-1]

A single crystal of Pd-(BOX-OH)-1 was mounted on a APEXII Bruker-AXS diffractometer for data collection (MoK_α radiation source, λ=0.71073 Å), at the Centre de Diffractométrie (CDIFX), Université de Rennes 1, France. The data were collected using SMART and the integration was performed using SAINT [155]. An empirical absorption correction was carried out using SADABS [156]. The structures were solved by direct methods with SHELXS-97 and refined by full-matrix least squares procedures on F^2 using the program SHELXL-97 [157]. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed at calculated positions using a riding model. Molecular graphic was generated using ORTEP-3 [158]. Crystal data and details of the data collection are summarized in (Table 2). Selected bond distances and bond angles are given in (Table 3).

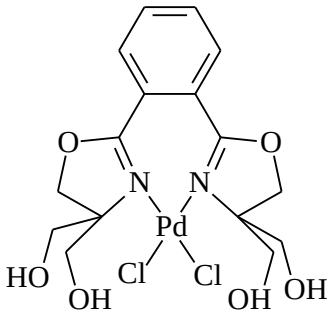
Table 2: Crystal and structure refinement data for Pd-(BOX-OH)-1

Empirical formula	$C_{16}\ H_{20}\ Cl_2\ N_2\ O_4\ Pd$
Formula weight	481.67
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system, space group	Monoclinic, C1c1
a (Å)	8.0720(3)
b (Å)	28.9624(13)
c (Å)	17.4283(8)
β (°)	89.9480(10)
Volume ($Å^3$)	4074.5(3)
Z, Calculated density ($g.cm^{-3}$)	4, 1.570
Absorption coefficient (mm^{-1})	1.194
F(000)	1936
Crystal size	0.580 x 0.230 x 0.120 mm
Crystal color	Yellow
Theta range (°)	3.491 to 27.516
h_min, h_max	-10, 10
k_min, k_max	-37, 37
l_min, l_max	-22, 22
Reflections collected / unique	35620 / 8783 [R(int) = 0.0459]
Reflections [I>2sigma(I)]	8700
Absorption correction type	multi-scan
Max. and min. transmission	0.867 , 0.682
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8783 / 2 / 452
Goodness-of-fit	1.039
Flack parameter	-0.04(2)
Final R indices [I>2sigma(I)]	R_1 = 0.0635, wR_2 = 0.1759
R indices (all data)	R_1 = 0.0640, wR_2 = 0.1770
Largest diff. peak, hole ($e.Å^{-3}$)	3.435, -1.524

Table 3: Selected bond distances (Å) and bond angles (°) for Pd-(BOX-OH)-1

Bond distances (Å)		Bond angles (°)	
Pd1- N1	2.035(11)	N1 - Pd1 - N2	87.8(4)
Pd1- N2	2.054(11)	N1 - Pd1 - Cl1	91.5(3)
Pd1 - Cl1	2.296(5)	N2 - Pd1 - Cl2	92.5(3)
Pd1 - Cl2	2.303(5)	Cl1 - Pd1 - Cl2	88.0(2)
N1 - C2	1.455(17)	C5 - N1 - C2	109.0(11)
N1 - C5	1.274(15)	C5 - O2 - C4	107.5(10)
O1 - C1	1.36(4)	C12 - N2 - C14	108.2(11)
O2 - C4	1.438(17)	C12 - O3 - C13	107.0(10)
O2 - C5	1.342(17)		
N2 - C12	1.288(16)		
N2 - C14	1.501(16)		
O3 - C12	1.316(15)		
O3 - C13	1.449(16)		
O4 - C16	1.39(3)		

2.3.2.3 [1,2-bis(4,4-dihydroxymethyl-2-oxazolinyl)benzene]chloride palladium(II) [Pd-(BOX-OH)-2]

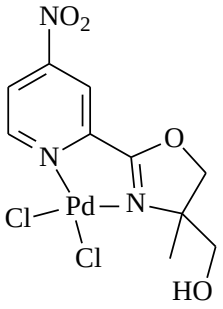


Pd-(BOX-OH)-2

Yellow solid; isolated yield (90 %); ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 7.81 (m, 2H, C*H*-4,5 arom), 7.62 (m, 2H, C*H*-3,6 arom), 4.62 (d, ^{2}J = 8.9 Hz, 2H, O-C*H*$_2$-4 oxazoline), 4.53 (d, ^{2}J = 8.6 Hz, 2H, O-C*H*$_2$-4 oxazoline), 4.33 (dd, ^{2}J = 6.1 Hz, ^{4}J = 5.9 Hz, 2H, *CH*$_2$*OH*), 3.94 (dd, ^{2}J = 6.9 Hz, ^{4}J = 6.1 Hz, 2H, *CH*$_2$*OH*), 3.89 (dd, ^{2}J = 6.9 Hz, ^{4}J = 6.1 Hz, 2H, *CH*$_2$*OH*) 3.79 (dd, ^{2}J = 7.0, Hz, ^{4}J = 6.3 Hz, 2H, *CH*$_2$*OH*);

^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 165.39 (C, *C-2-oxazoline*), 162.78 (C, *C-2-oxazoline*), 133.00 (C, *C-1- arom*), 130.55 (C, *C-2-arom*), 129.81 (C, *C-3-arom*), 129.70 (C, *C-6-arom*), 128.11 (C, *C-4-arom*), 125.96 (C, *C-5-arom*), 78.22 (C, *C-5-oxazoline*), 77.48 (C, *C-5-oxazoline*), 74.83 (C, *C-4-oxazoline*), 71.10 (C, *C-4-oxazoline*), 64.01 (C, HO-CH_2 x2), 63.30 (C, HO-CH_2), 62.86 (C, HO-CH_2); IR (*cm^{-1}*) 3485, 1646, 1029; Anal. Calc. for $C_{16}H_{20}$ $Cl_2N_2O_6Pd$, (513.67): C, 37.41; H, 3.92; N, 5.45. Found: C, 34.73; H, 3.86; N, 5.39.

2.3.2.4 4-Nitro-2-(4-hydroxymethyl-4-methyl)-2-oxazolinylpyridine)chlorido palladium(II) [Pd-OX-Pyr-OH]



Pd-OX-Pyr-OH

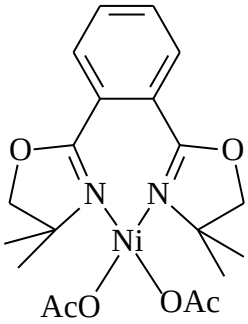
Yellow power; isolated yield (76%); ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 9.36 (d, ^{3}J = 4.2 Hz, H, 6-Pyr), 8.61 (s, H, 3-Pyr), 8.38 (d, ^{3}J = 4.1 Hz, H, 5-Pyr), 5.38 (d, ^{2}J = 5.7 Hz, H, *5-oxazolinyl*), 4.94 (d, ^{2}J = 5.9 Hz, H, *5-oxazolinyl*), 4.53 (d, ^{2}J = 5.4 Hz, H, *4-hydroxymethyl-oxazolinyl*) 4.03 (d, ^{2}J = 5.3 Hz, H, *4-hydroxymethyl-oxazolinyl*), 1.50 (s, 3H, *4-methyl-oxazolinyl*). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 168.08 *(N=CO)*, 155.17 (*C, 6-Pyr*), 153.17 (*C, 2-Pry*), 146.80 (*C, 4-Pyr*), 123.12 (*C, 3-Pyr*), 119.05 (*C, 5-Pyr*), 79.68 (*C, 5-Oxazolinyl*), 73.31 (*CH_2OH*), 64.89 (*C, 4-Oxazolinyl*), 21.76 (*CH_3*);

IR (cm^{-1}) 3396, 1606, 1592, 1540, 1084, 1058; Anal. Calc. for $C_{10}H_{11}N_3O_4Cl_2Pd$, (414.54): C, 28.97; H, 2.67; N, 10.14. Found: C, 28.23; H, 2.59; N, 10.09.

2.3.3 Characterizations of nickel(II) bis(oxazoline) (Ni-BOX) complexes

The characterization of the nickel(II)-BOX complexes, unlike that of the palladium(II)-BOX complexes, was carried out employing FTIR and EA only as characterization techniques. The NMR (^1H and ^{13}C) spectra were observed to be broad due to the paramagnetic property exhibited by these complexes, while the crystals of these complexes were attempted in various solvent systems but could not be afforded. The details of the characterization of the Ni-BOX-A and Ni-(BOX-OH)-1 complexes are given below.

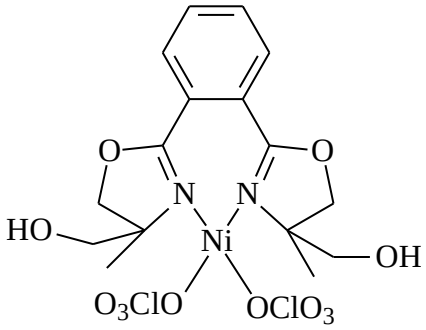
2.3.3.1 [1,2-bis (4,4-dimethyl-2-oxazolinyl)benzene]acetato nickel(II) (Ni-BOX-A)



Ni-BOX-A

Green solid; isolated yield (90%); IR (cm^{-1}) 1639, 1450, 1060; Anal. Calc. for $C_{20}H_{26}N_2O_6Ni$, (449.13): C, 36.26; H, 3.80; N, 5.29. Found: C, 38.23; H, 3.59; N, 4.79.

2.3.3.2 [1,2-bis(4-hydroxymethyl-4-methyl-2-oxazolinyl)benzene]perchlorato nickel(II) [Ni-(BOX-OH)-1]



Ni-(BOX-OH)-1

Pale green solid; isolated yield (90 %); IR (*cm^{-1})* 3373, 1639, 1144, 1112, 1065; Anal. Calc. for $C_{16}H_{20}Cl_2N_2O_{12}Ni$, (561.94): C, 34.20; H, 3.59; N, 5.00. Found: C, 33.77; H, 3.54; N, 4.69.

2.4 Discussion

2.4.1 Characterization of BOX-OH

The preparation of the ligands BOX-OH-1 and BOX-OH-2 (Figure 18), OX-COOH (Figure 19) and OX-Pry-OH (Figure 20) was successfully carried out. The bis(hydroxymethyloxazolines) were prepared by treating the phthalonitrile or its derivative with 2 equivalent of aminoalcohol catalyzed by zinc triflate. The corresponding BOX-OH compounds were isolated in appreciable yields. The bis(oxazolines) (BOX-OH-1, BOX-OH-2 and BOX-OH-3) showed ^{1}H and ^{13}C NMR chemical shifts that were consistent with the structures proposed as shown in the experimental section above. While OX-Pry-OH was prepared by the reaction of the

aminoalcohol and the corresponding nitrile (1:1). OX-COOH was synthesized by the reaction of phthalic acid and the corresponding amino phenol (1:1) under the specified condition in section 2.2. The products were isolated, purified and characterized using ^{1}H and ^{13}C NMR, EA, GC-MS, and FTIR. These characterization data were found to be consistent with the proposed structure.

2.4.1.1 [1,2-bis (4-hydroxymethyl-4-methyl-2-oxazolinyl)benzene] (BOX-OH-1)

The compound BOX-OH-1 was prepared from (2-amino-2-hydroxymethanyl-propane-1-ol) and phthalonitrile. It was purified by employing ethyl acetate / methanol (9:1) as a solvent system in silica gel column chromatography to produce a pure white crystalline solid product. The ^{1}H NMR gave the integration that were consistent with the number of protons in the BOX-OH-1 ligand, 4 protons in the aromatic region at 7.66 ppm and 7.56 ppm each with integration that corresponds to 2 protons, 6 protons for the peak around 1.22 ppm consistent with the two methyl groups on the oxazoline rings, 2 protons for the methylenes of the oxazoline rings and 2 protons for the hydroxymethane attached to the oxazoline rings (Figure 23).

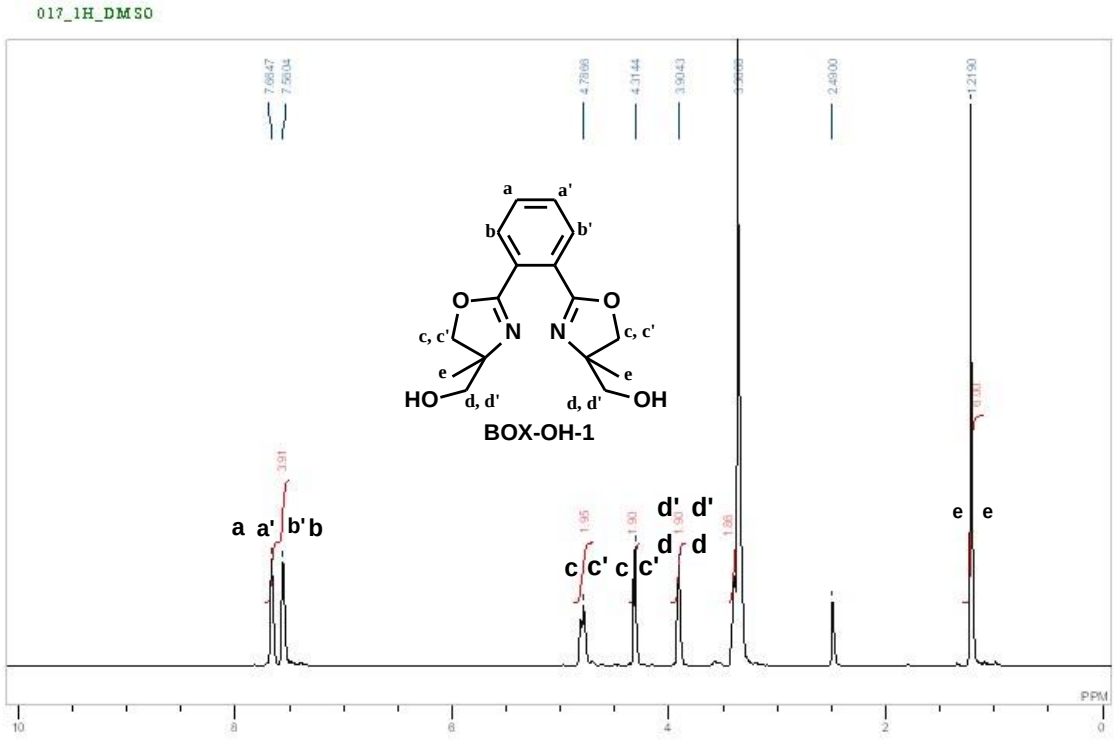


Figure 23: The ^{1}H NMR spectrum of the BOX-OH-1 ligand

Also, the ^{13}C NMR has number and the positions of the carbons that are consistent with that of the prepared BOX-OH-1 ligand (Figure 24).

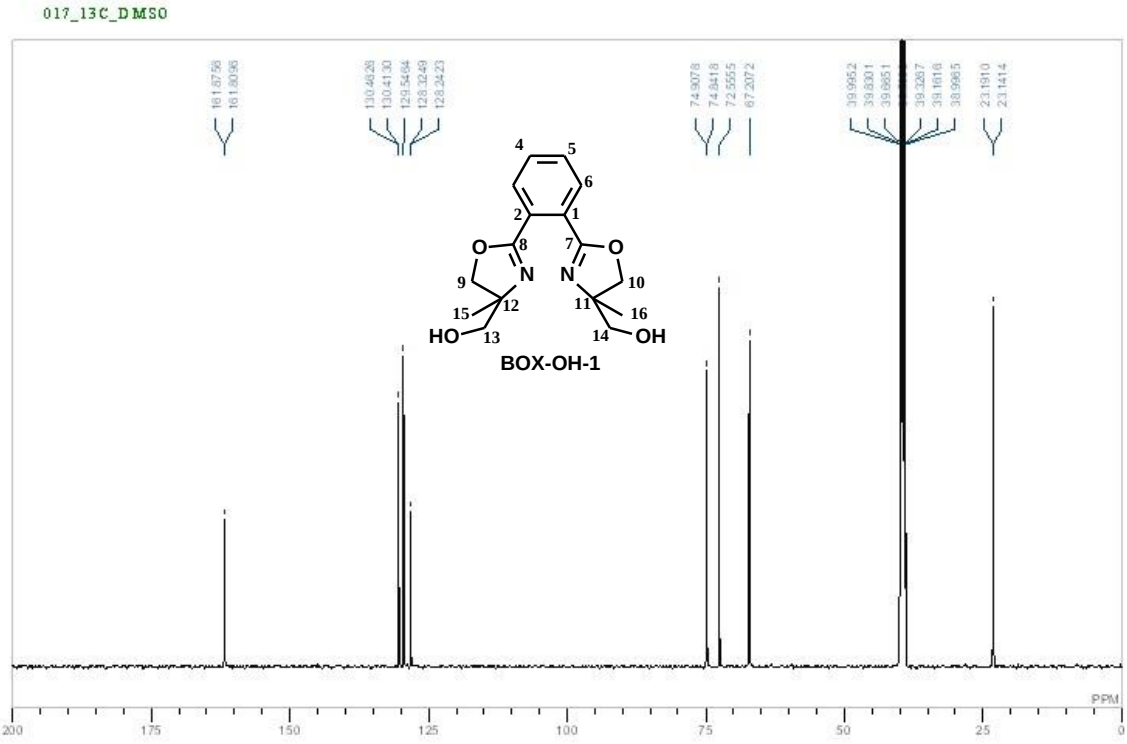


Figure 24: The ^{13}C NMR spectrum of the BOX-OH-1 ligand

Furthermore, the FTIR analysis results gave the frequency bands that are consistent with that of the functional groups present in the BOX-OH-1 ligand: 3370 cm^{-1} (O-H), 1661 cm^{-1} (C=N), 1085 cm^{-1} (C-O alcohol), 1050 cm^{-1} (C-O oxazoline) (Figure 25).

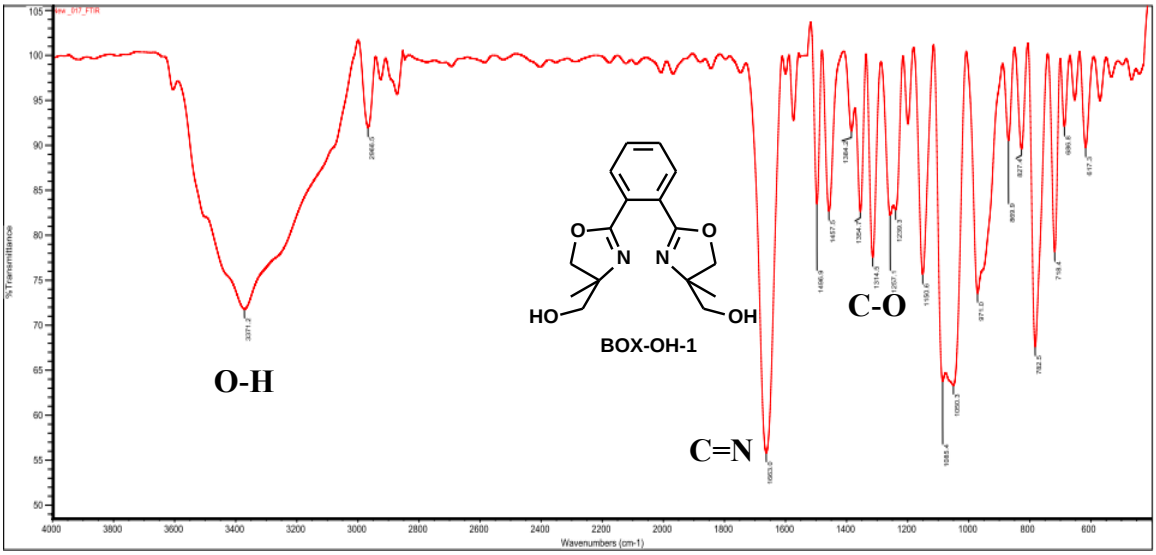


Figure 25: The FTIR spectrum of the BOX-OH-1 ligand

Elemental analysis data was found to be consistent with theoretically calculated mass composition, hence, confirming the formation of this BOX-OH-1 ligand with the structure proposed.

2.4.1.2 [1,2-bis(4,4-dihydroxymethyl-2-oxazolinyl) benzene] (BOX-OH-2)

The compound BOX-OH-2 was prepared from trizma base (2-amino-2-hydroxymethanyl-propane-1,3-diol) and phthalonitrile. It was purified by employing the solvent system ethyl acetate / methanol (8/2) in silica gel column chromatography to give a pure pale yellow crystalline product. ^{1}H NMR gave the integration that were consistent with the number of protons in the BOX-OH-2 ligand, 4 protons in the aromatic region at 7.77 and 7.58 ppm each with an integration for 2 protons, which is consistent with that on the benzene ring of the BOX-OH-2 ligand, 8 protons for the peak between 3.50-3.46 ppm

consistent with the methylenes of the hydroxymethyl groups attached on the oxazoline rings, 2 protons for the methylenes of the oxazoline rings at 4.68 ppm (Figure 26).

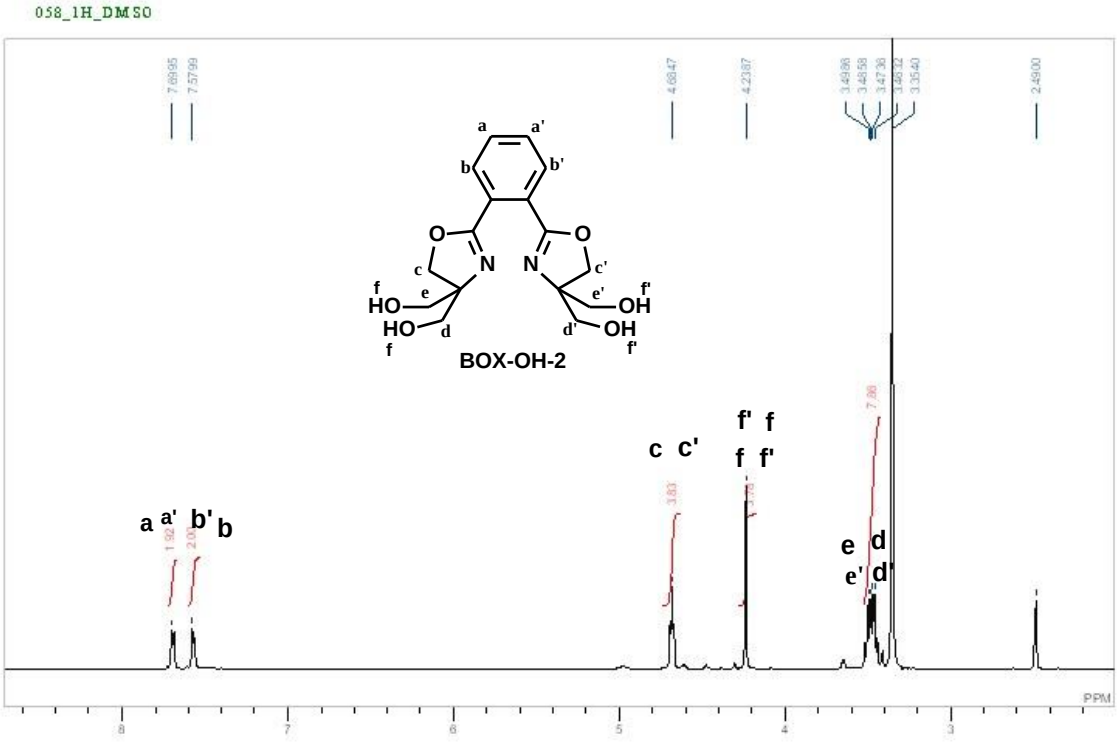


Figure 26: The ^{1}H NMR spectrum of the BOX-OH-2 ligand

In addition, the ^{13}C NMR has the exact number of carbons (16) consistent with the structure of the proposed BOX-OH-2 ligand and as indicated in the spectral data of the compound (Figure 27).

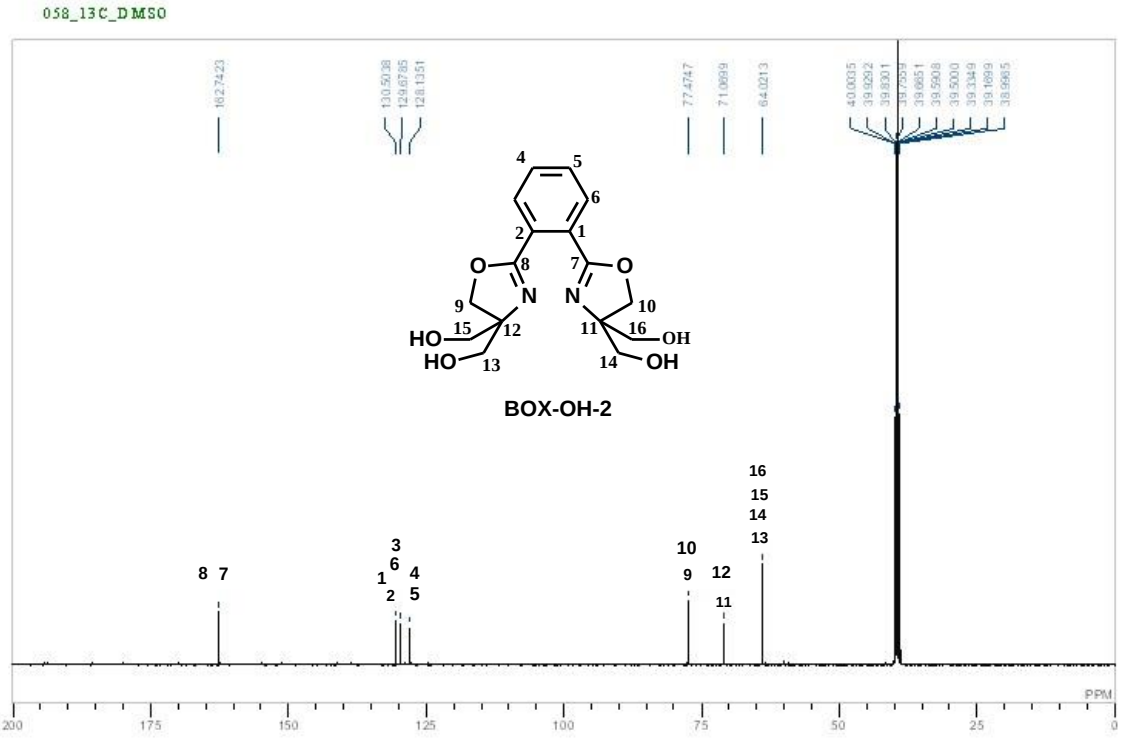


Figure 27: The ^{13}C NMR spectrum of the BOX-OH-2 ligand

It was observed that there were seven peaks representing the 16 carbons; 64.02 ppm with the highest intensity, representing all the for hydroxymethyl carbons, 71.07 ppm for 4th carbons of the two oxazoline rings, 77.47 ppm for 5th carbons of the two oxazoline rings, while 130.50 ppm, 129.68 ppm, and 128.13 ppm were assigned to carbons number 1 and 2, 3 and 6, 4 and 5 of the benzene ring spacer respectively, and finally 2nd carbons of the two oxazoline rings was assigned to 162.74 ppm confirming the formation of the BOX-OH-2 ligand as proposed. Moreover, the FTIR analysis results gave bands that are consistent with the functional groups present in the BOX-OH-2 ligand: 3401 cm^{-1} (O-H), 1665 cm^{-1} (C=N), 1088 cm^{-1} (C-O alcohol), 1052 cm^{-1} (C-O oxazoline) (Figure 28).

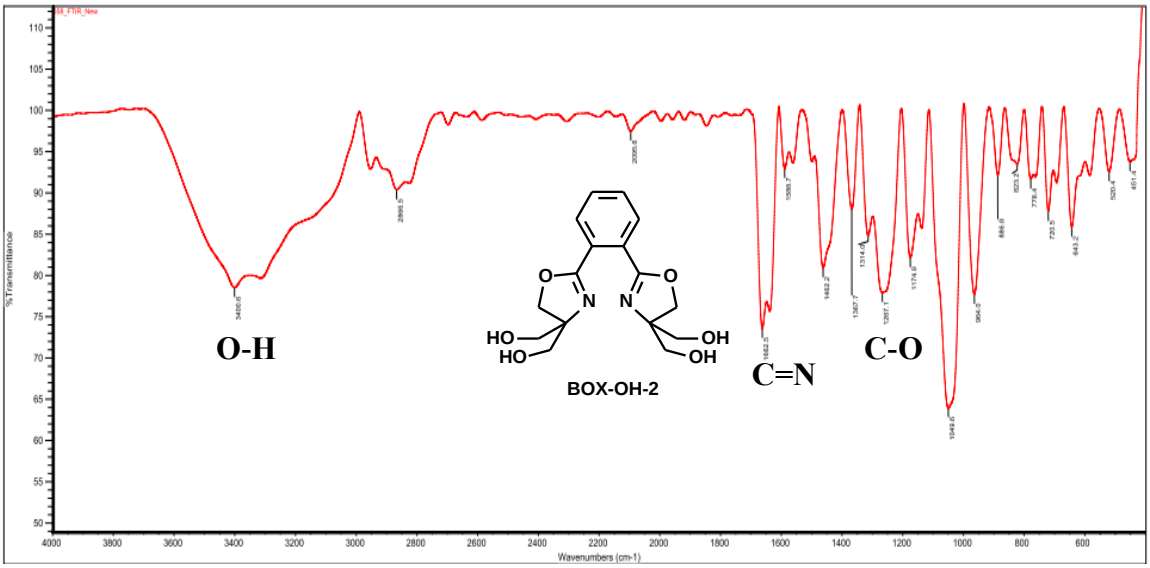


Figure 28: The FTIR spectrum of the BOX-OH-2 ligand

The elemental analyses data were also consistent with theoretically calculated mass composition confirm the formation of this ligand.

2.4.1.3 *o*-[2-Benzo-2-oxazolinyl] benzoic acid (OX-COOH)

The compound OX-COOH was prepared from phthalic acid and 2-aminophenol. It was purified by employing ethyl acetate:hexane (3:7) as a solvent system in silica gel column chromatography to give a pure brown solid product. The ^{1}H NMR gave the integrations that were consistent with the number of protons in the OX-COOH ligand, with the characteristic carboxylic acid proton peak shown at10.21 ppm, 4 protons in the aromatic region at 7.90 - 7.85 ppm, which were consistent with the number of protons on the benzene ring of the OX-COOH ligand, a triplet at 7.30-7.27 ppm indicating the proton on *5-benzo-oxazolinyl*, doublet at 7.18-7.17 ppm and 6.96-9.64 ppm, which are consistent

with the protons on *7-benzo-oxazolinyl* and *4-benzo-oxazolinyl*, respectively, and finally, a triplet at 6.92-6.89 for the proton on *6-benzo-oxazolinyl* (Figure 29).

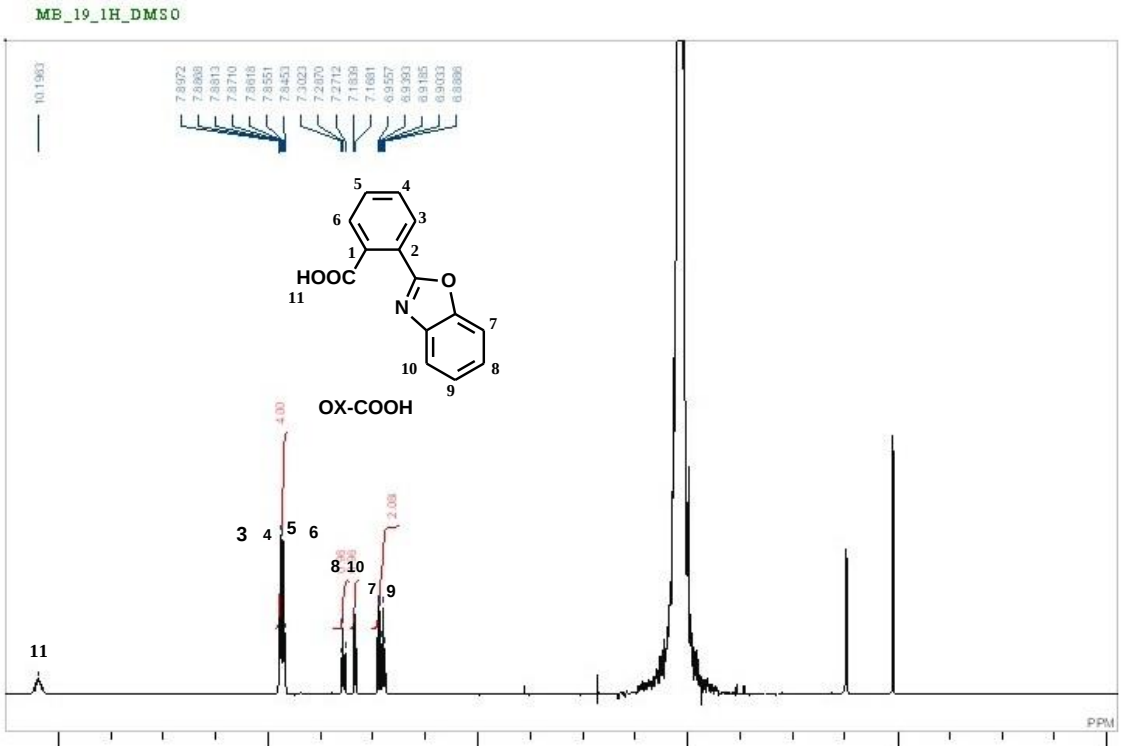


Figure 29: The ^{1}H NMR spectrum of the OX-COOH ligand

The ^{13}C NMR has number of carbons that are consistent with that of the OX-COOH ligand as indicated in the spectral data (Figure 30).

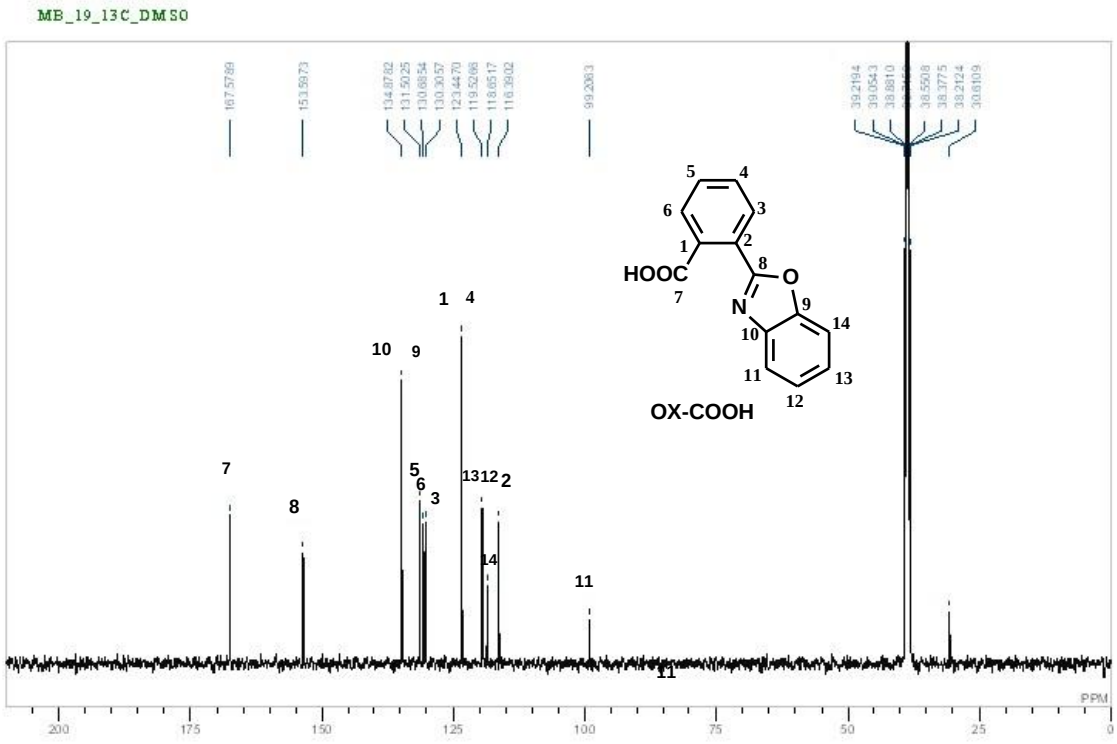


Figure 30: The ^{13}C NMR spectrum of the OX-COOH ligand

Furthermore, the FTIR results gave bands that are consistent with that of the functional groups present in the OX-COOH ligand: 3380 cm^{-1} (O-H of the COOH), 1702 cm^{-1} (C=N) 1100 cm^{-1} (C-O of the COOH), 1085 cm^{-1} (C-O oxazoline) (Figure 31).

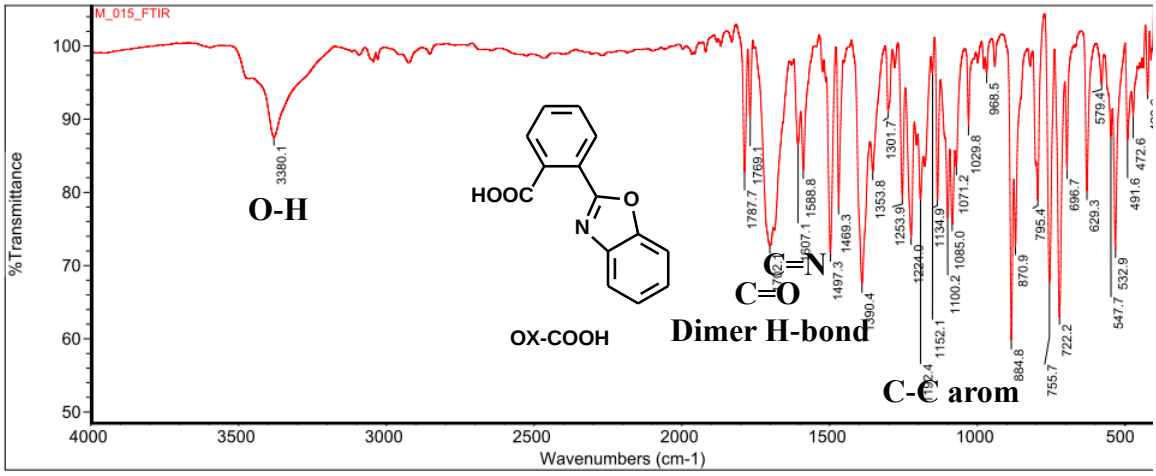


Figure 31: The FTIR spectrum of the OX-COOH ligand

The elemental analyses data and the GC-MS data were consistent with theoretically calculated mass composition and the proposed molecular mass of this ligand.

2.4.1.4 4-Nitro-2-(4-hydroxymethyl-4-methyl)-2-oxazolinylpyridine (Pyr-OX-OH)

The compound Pyr-OX-OH was prepared from (2-amino-2-hydroxymethanyl-propane-1-ol) and phthalonitrile. It was purified by employing ethyl acetate/methanol (9:1) solvent system in silica gel column chromatography to give a pure pale brown oily product. The ^{1}H NMR gave the integration that were consistent with the number of protons in the Pyr-OX-OH ligand: 3 protons in the aromatic region; a doublet at 9.00 ppm corresponding to the proton on carbon number 6 of the pyridine ring, a singlet at 8.68 ppm for carbon number 3 of the pyridine ring and another doublet at 8.15 ppm corresponding to the proton on carbon number 5 of the pyridine ring, each with an integration of 1, which is consistent with the structure on the pyridine ring of the Pyr-OX-OH ligand. An integration of 1 each for the peak observed between 4.65 ppm and 3.56 ppm regions was observed, each having a doublet at 4.65 ppm corresponding to the one proton of methylene on the oxazoline coupling with the other methylene proton, 4.25 ppm corresponds to the second proton of methylene on the oxazoline coupling with the first proton, 3.85 ppm corresponds to the one proton of methylene on the hydroxymethene substituent of the oxazoline coupling with the other methylene proton and 3.56 ppm corresponds to the second proton of methylene on the hydroxymethene substituent of the oxazoline coupling with the first methylene proton. The peak at 1.40 is an intense singlet with integration of 3, corresponding to the methyl group on the oxazoline rings (Figure 32).

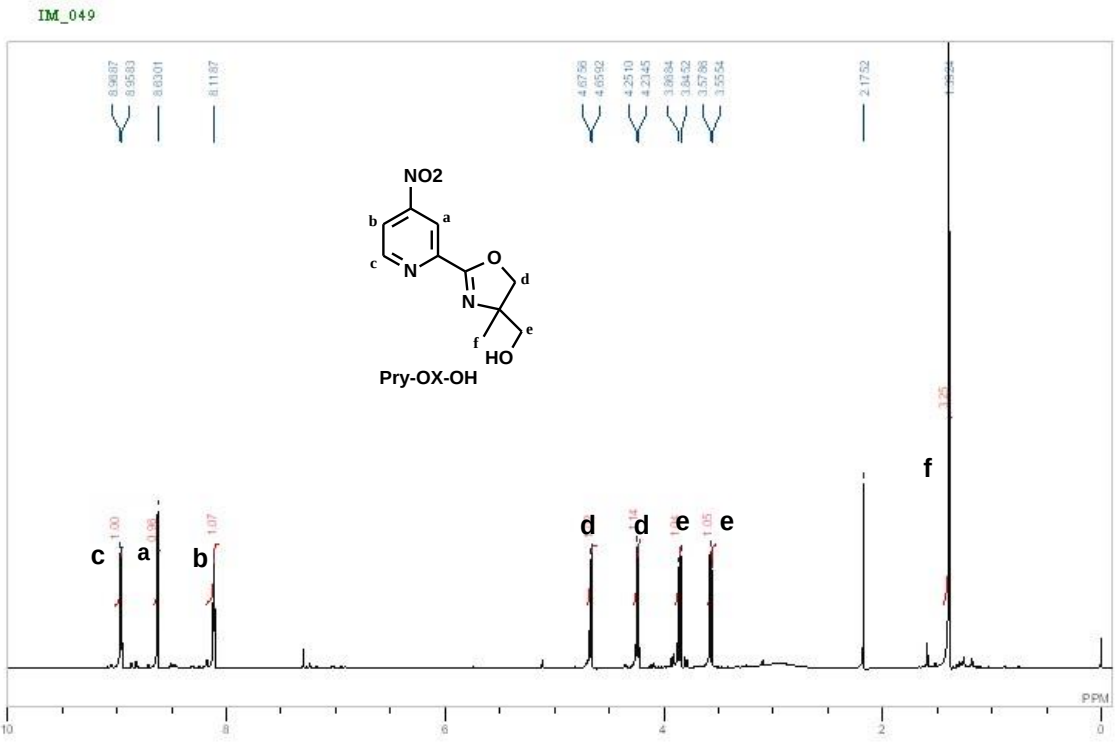


Figure 32: The ^{1}H NMR spectrum of the OX-Pyr-OH ligand

Also, the ^{13}C NMR has 10 peaks, each corresponding to one carbon atom, which is exactly the number of carbons that are consistent with that of the prepared Pyr-OX-OH ligand. 5 Aromatic carbons were found within the aromatic region (154.17 - 116.62 ppm), the methyl group at 23.38 ppm, carbons attached to electronegative atoms (N and O) found in the range (75.72 - 67.86 ppm) and the most deshielded carbon (i.e. one between C and N atoms) was assigned at 161.29 ppm. This clearly indicates the formation of the Pyr-OX-OH ligand having the expected structure (Figure 33).

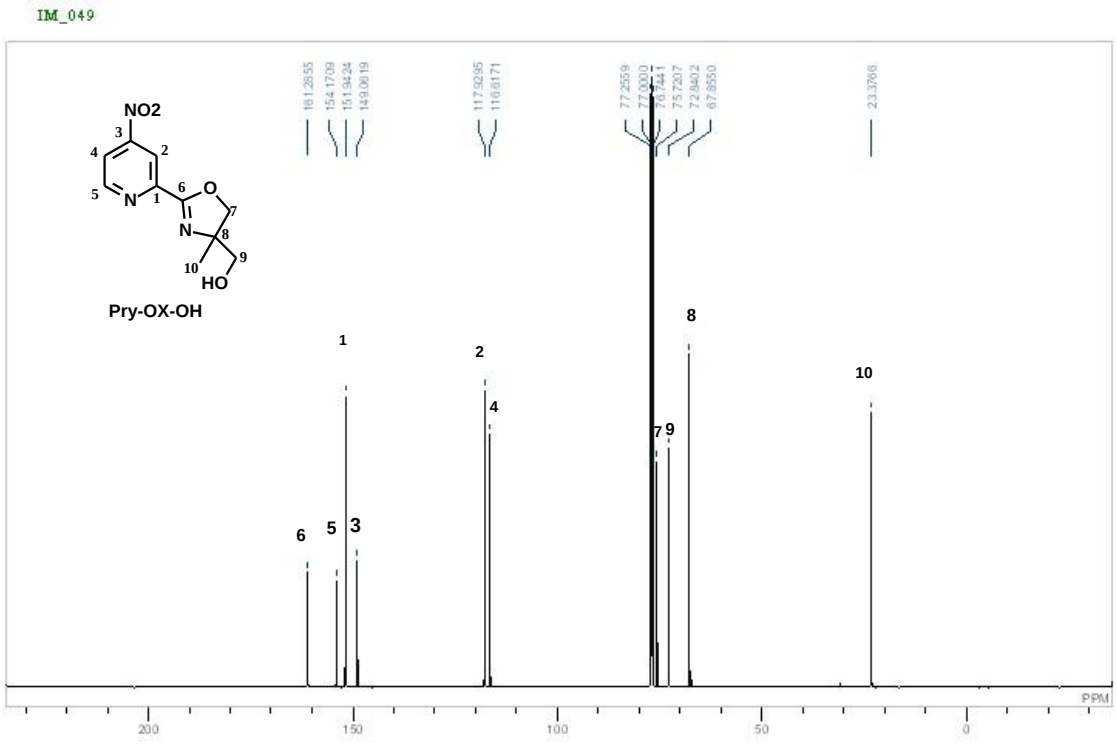


Figure 33: The ^{13}C NMR spectrum of the OX-Pyr-OH ligand

Furthermore, the results of the FTIR analysis showed the frequency bands consistent with that of the functional groups present in the Pyr-OX-OH ligand: 3370 cm^{-1} (O-H), 1661 cm^{-1} (C=N) 1085 cm^{-1} (C-O alcohol), 1050 cm^{-1} (C-O oxazoline)

Elemental analysis data was found to be consistent with theoretically calculated mass composition, hence, confirming the formation of this Pyr-OX-OH ligand with the structure proposed.

2.4.2 Characterization of palladium(II) BOX-OH complexes

The palladium(II) bis(hydroxymethyloxazoline) complexes, Pd-(BOX-OH)-1, Pd-(BOX-OH)-2 and Pd-(BOX-OH)-3, were prepared from the reactions of BOX-OH compounds (BOX-OH-1, BOX-OH-2 and BOX-OH-3) with palladium(II) chloride (Figure 21). 4-nitro-2-(4-hydroxymethyl-4-methyl)-2-oxazolinylpyridine)chlorido palladium(II) (Pd-OX-Pyr-OH) was synthesized by the reaction of 4-nitro-2-(4-hydroxymethyl-4-methyl)-2-oxazolinylpyridine (OX-Pyr-OH) compound with palladium(II) chloride (Figure 22).

2.4.2.1 [1,2-bis(4-hydroxymethyl-4-methyl-2-oxazolinyl)benzene]chlorido palladium(II) [Pd-(BOX-OH)-1]

The palladium complex Pd-(BOX-OH)-1 was prepared from the reaction of BOX-OH-1 with palladium(II) chloride. The complex was purified by recrystallization from dimethylformamide (DMF). A single crystal suitable for X-ray was successfully grown from DMF solution after a slow evaporation at room temperature. The complex obtained was observed to be clear yellow needle shape air stable crystals. The coordination of the $PdCl_2$ precursor with the BOX-OH-1 ligand was also confirmed based on ^{1}H and ^{13}C NMR. Indeed, all the proton and carbon resonances have shifted in a certain scale as compared to their position in the free BOX-OH-1 ligand. In fact, the peak at 1.22 ppm which is a singlet with an integration of six, corresponding to the two equivalent methyl groups in the ^{1}H NMR of the free BOX-OH-1 ligand, gave two separate singlets, one at 1.63 ppm with integration of three, indicating three protons of one methyl group, and the other at 1.47 ppm also with an integration of three, corresponding to the other three protons in the Pd-(BOX-OH)-1 complex. This clearly shows that the two equivalent

methyl groups of the BOX-OH-1 ligand were no longer equivalent after the Pd-(BOX-OH)-1 complex was formed. In addition, the hydroxymethyl group peaks of the BOX-OH-1 ligand appeared at 3.90 ppm and 3.40 ppm both as singlet with an integration of 2 each. However, when the Pd-(BOX-OH)-1 complex was formed, the protons of the hydroxymethyl groups become non-equivalent, each giving a clear doublet. Furthermore, the aromatic protons resonance shifted from 7.56 ppm and 7.66 ppm in the BOX-OH-1 ligand to 7.82 ppm and 7.92 ppm in the Pd-(BOX-OH)-1 complex ((Figure 34).

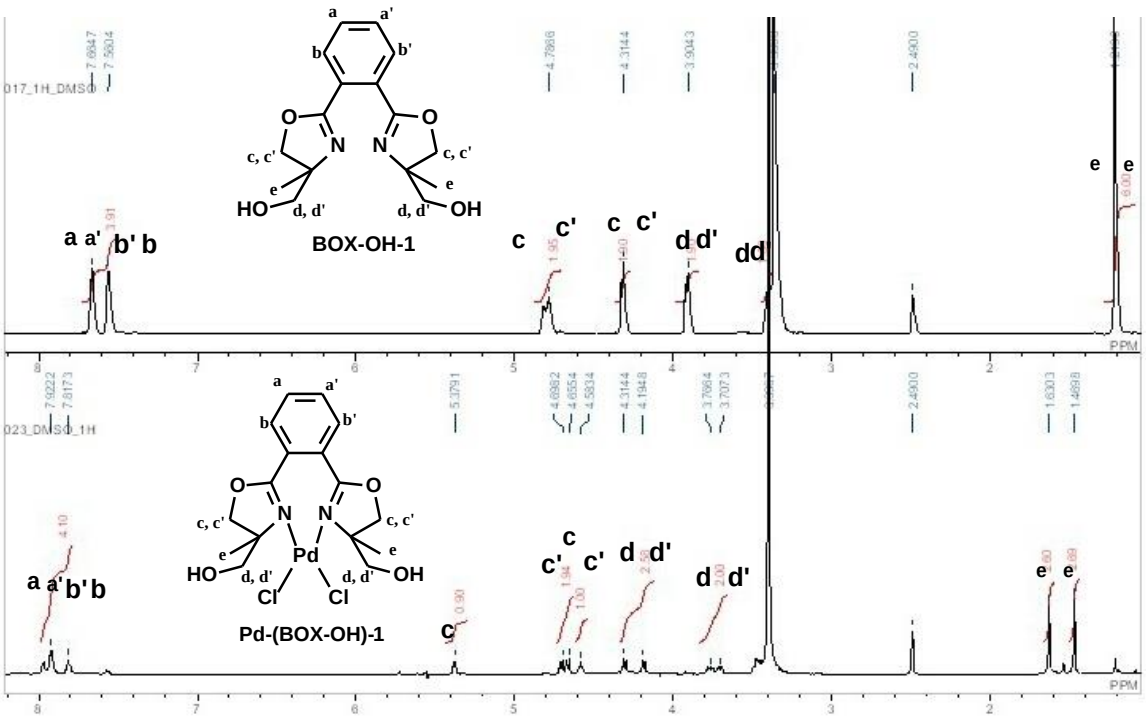


Figure 34: The ^{1}H NMR spectra of the BOX-OH-1 ligand (above) and the corresponding Pd-(BOX-OH)-1 (below) complex

Also, the ^{13}C NMR showed an interesting pattern which clearly indicates the formation of complex. The free BOX-OH-1ligand gave eight singlet carbon resonance peaks,

indicating the symmetric nature of the BOX-OH-1 compound. However, after the complexation with palladium(II), all peaks became doublet with a little shift as compared to the BOX-OH-1 ligand. This shows that the symmetry of the compound was distorted after the complex was formed; hence, all the sixteen carbons in the Pd-(BOX-OH)-1 are non-equivalent (Figure 35).

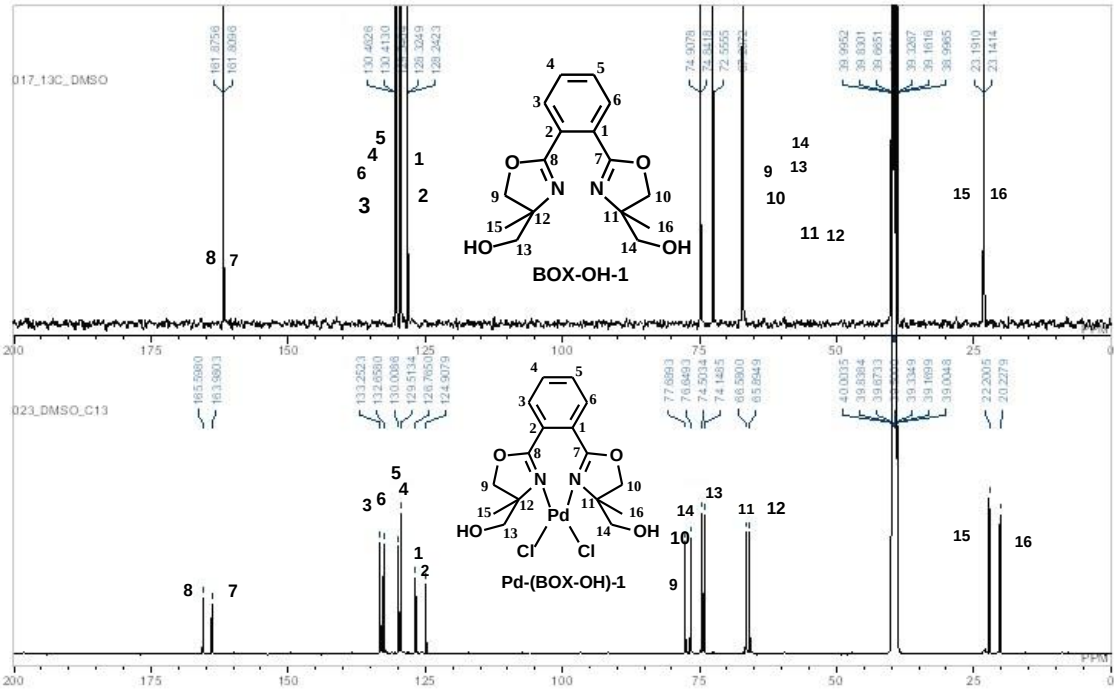


Figure 35: The ^{13}C NMR spectra of the BOX-OH-1 ligand (above) and the corresponding Pd-(BOX-OH)-1 (below) complex

Furthermore, FTIR data of both the ligand and the complex were also used as a measure to indicate the formation of Pd-(BOX-OH)-1 from BOX-OH-1. The shift in the position of *C=N* band from 1663 cm^{-1} in the spectrum of BOX-OH-1 ligand to 1643 cm^{-1} in the spectrum of Pd-(BOX-OH)-1 is was attributed to the decrease in bond character of the *C=N* bond. Also, the *C-O* band, observed at 1355 cm^{-1} in the ligand was increase to

1378 cm^{-1} due to increase in bond character of the *C-O* bond after coordination. These are clear indications of coordination between the ligand the palladium (Figure 36).

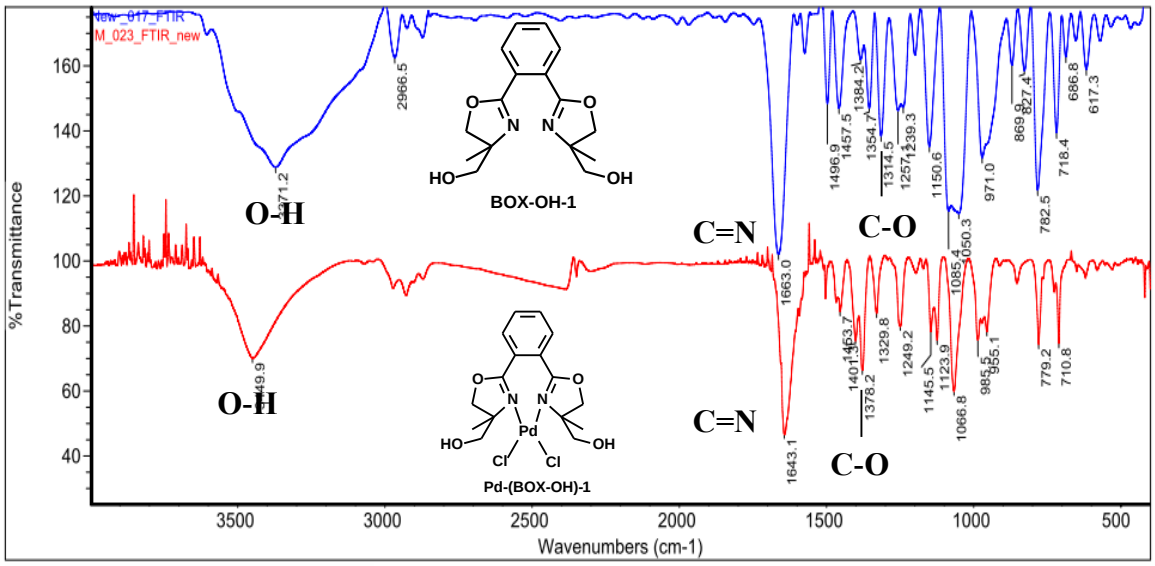


Figure 36: The FTIR spectra of the BOX-OH-1 ligand (above) and the corresponding Pd-(BOX-OH)-1 (below) complex

Finally, the crystal structure of the complex obtained (Figure 37) confirms the formation of Pd-(BOX-OH)-1.

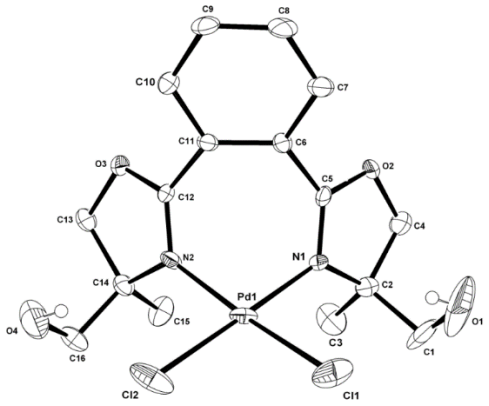


Figure 37: Ortep diagram of Pd-(BOX-OH)-1 showing the atomic labeling scheme. Thermal ellipsoids are drawn at 30 % probability level. Hydrogen atoms, except hydroxyl H atoms, have been omitted for clarity

2.4.2.2 [1,2-bis(4,4-dihydroxymethyl-2-oxazolinyl)benzene]chlorido palladium(II) [Pd-(BOX-OH)-2]

The palladium complex Pd-(BOX-OH)-2 was prepared from the reaction of BOX-OH-2 with palladium(II) chloride in DMF. The complex was washed with dichloromethane to remove the excess ligand. The complex was obtained in form of yellow and air stable powder. The formation of Pd-(BOX-OH)-2 by the coordination of the BOX-OH-2 ligand with $PdCl_2$ was confirmed by ^{1}H and ^{13}C NMR and other characterization techniques. Interestingly, shifts were observed in all the protons and carbon resonances to a certain scale relative to their positions in the free ligand. The ^{13}C NMR spectra of the complex gave an excellent and convincing indication of the complex formation. There are total of 16 carbons in both the ligand and the complex. In the ligand free form, there were seven peaks representing the 16 carbons: 64.02 ppm with the highest intensity, representing all the hydroxymethyl carbons, 71.07 ppm for 4th carbons of the two oxazoline rings, 77.47 ppm for 5th carbons of the two oxazoline rings, while 130.50 ppm, 129.68 ppm, and 128.13 ppm were assigned to carbons number 1 and 2, 3 and 6, 4 and 5 of the benzene ring spacer, respectively, and finally the 2^{nd} carbons of the two oxazoline rings was assigned to 162.74 ppm. However, 15 separate peaks were observed in the complex, each standing for a carbon atom in the complex, except the peak at 64.01 ppm, which is the most intense peak and represents two carbons one each from the hydroxymethylene group from the two oxazoline ring. This splitting of peaks indicates the formation of Pd-(BOX-OH)-2 complex and that the carbons are non-equivalent as they were in the free ligand (Figure 38).

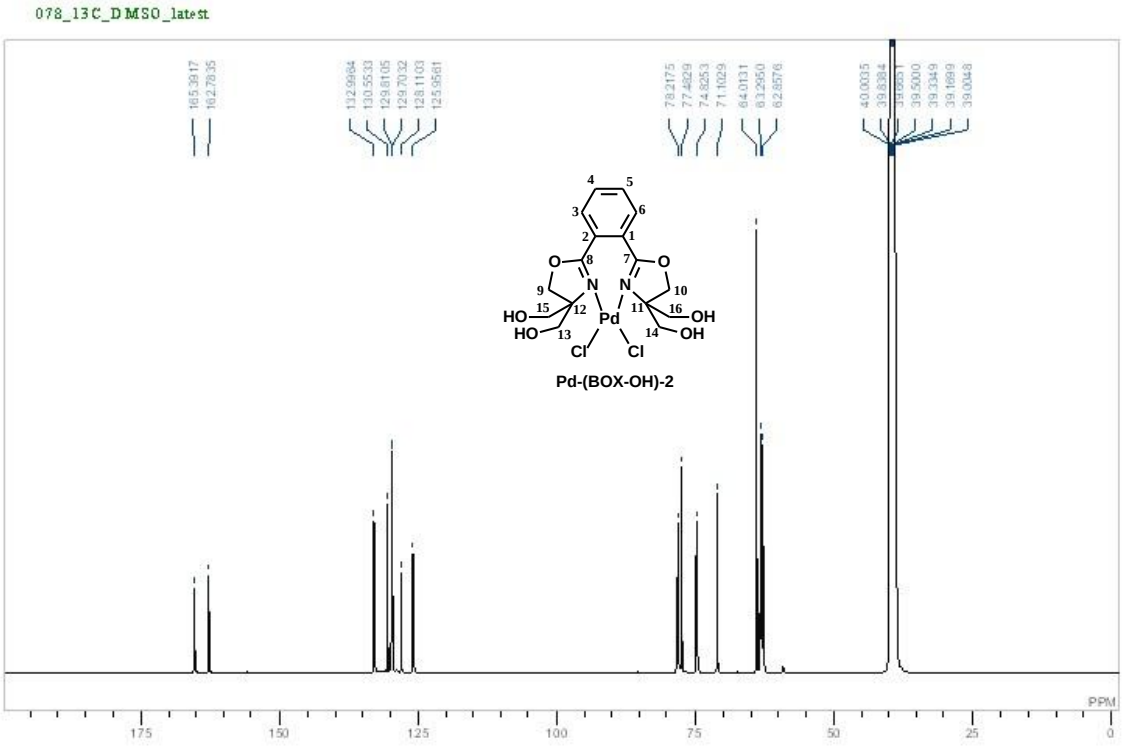


Figure 38: The ^{13}C NMR spectra of the Pd-(BOX-OH)-2 complex

The formation of Pd-(BOX-OH)-2 from BOX-OH-2 was further rationalized from the respective FTIR data of both the ligand and the complex. The shift in the position of *C=N* band from 1665 cm^{-1} in the spectrum of BOX-OH-1 ligand to 1646 cm^{-1} in the spectrum of Pd-(BOX-OH)-1 is an indication that the ligand has been coordinated to the palladium center (Figure 39).

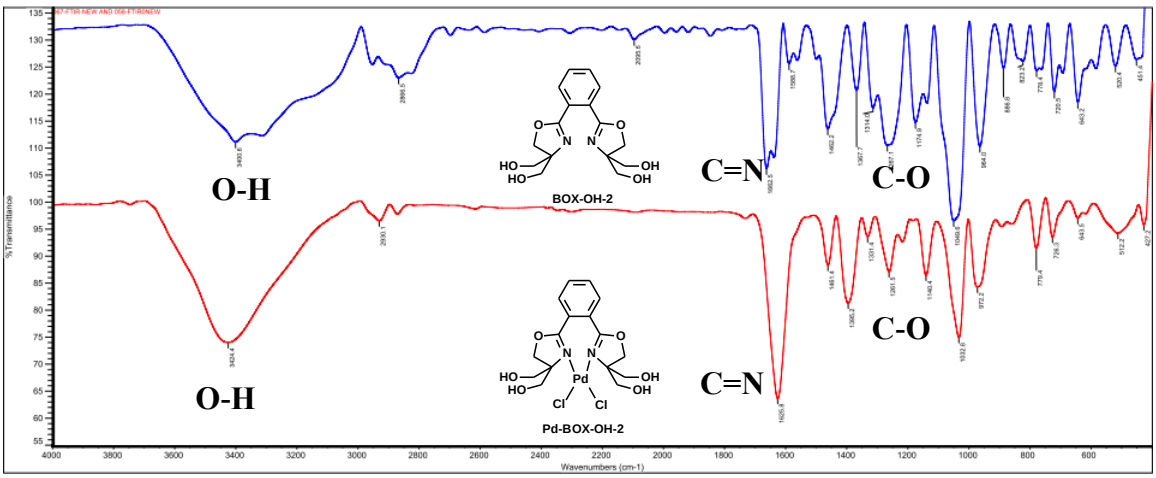


Figure 39: The FTIR spectra of the BOX-OH-2 ligand (above) and the corresponding Pd-(BOX-OH)-2 (below) complex

The elemental analysis results also showed a close agreement with the theoretical mass.

2.4.2.3 4-nitro-2-(4-hydroxymethyl-4-methyl)-2-oxazolinylpyridine)chlorido palladium(II) (Pd-Pyr-OX-OH)

The palladium(II)-oxazolinylpyridine complex, Pd-Pyr-OX-OH, was prepared from the reaction of oxazolinylpyridine, Pyr-OX-OH, compound and palladium(II) chloride. The obtained complex was a dim yellow and air stable powder. ^{1}H and ^{13}C NMR were employed to characterize and confirm the formation of the palladium complex from Pyr-OX-OH ligand and $PdCl_2$ precursor. Indeed, all the protons and carbon resonances in the complex have shifted relative to their positions in the free ligand. Interestingly, there was no much ambiguity in assigning the peaks; the methyl protons which appeared at 1.39 ppm in the free ligand shifted to 1.50 ppm in the complex. Also, methylene protons, which appear as doublets at 4.67 ppm, 4.24 ppm, 3.86 ppm and 3.57 ppm with integration of 1 each in the ligand, have shifted to 5.38 ppm, 4.94 ppm, 4.53 ppm and 4.03 ppm in the complex, respectively. Furthermore, the three aromatic protons on pyridine shifted

significantly downfield relative to their positions in the free ligand, except the proton on carbon 3 of the pyridine that was shifted upfield relative to the free ligand and was shifted negligibly from 8.63 ppm in free ligand to 8.61 ppm in the complex (Figure 40).

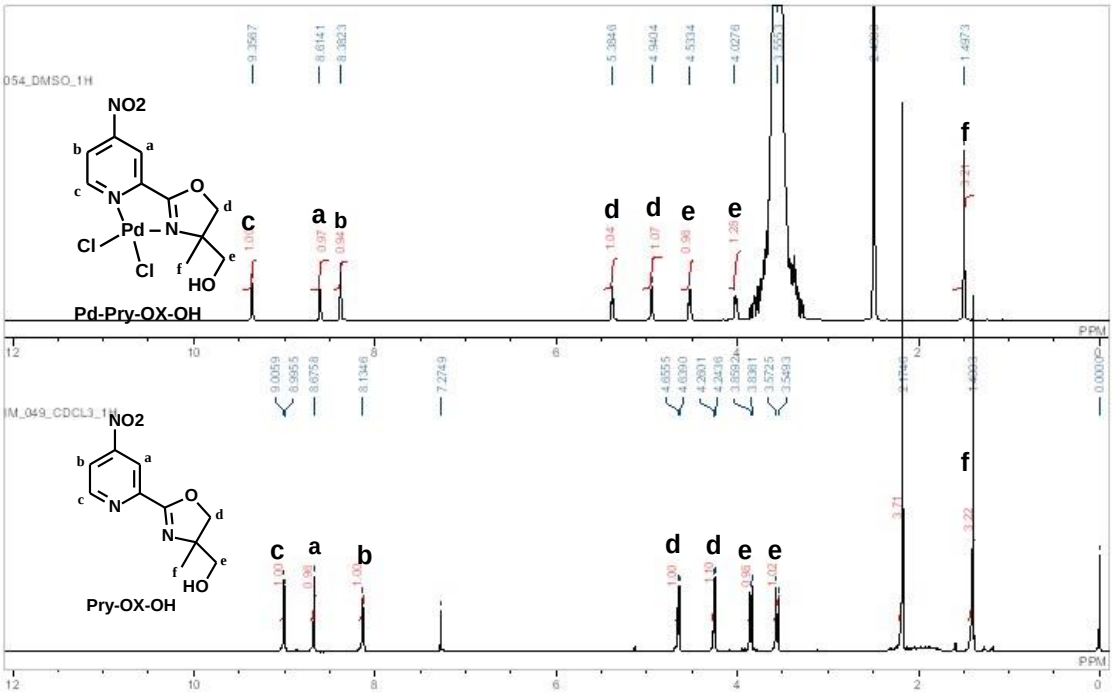


Figure 40: The ^{1}H NMR spectra of the Pyr-OX-OH ligand (above) and the corresponding Pd-Pyr-(OX-OH) (below) complex

The carbon of the methyl group, which appeared at 23.38 ppm in the ligand, was shifted to 21.76 ppm in the complex. Also, the carbon atom attached directly to both nitrogen and oxygen atom of the oxazoline ring was observed to be more downfield in the complex (168.08 ppm) than in the ligand (161.29 ppm). This is a clear indication that there was a complex formation, and that the nitrogen is involved in this coordination thereby deshielding more the carbon (Figure 41).

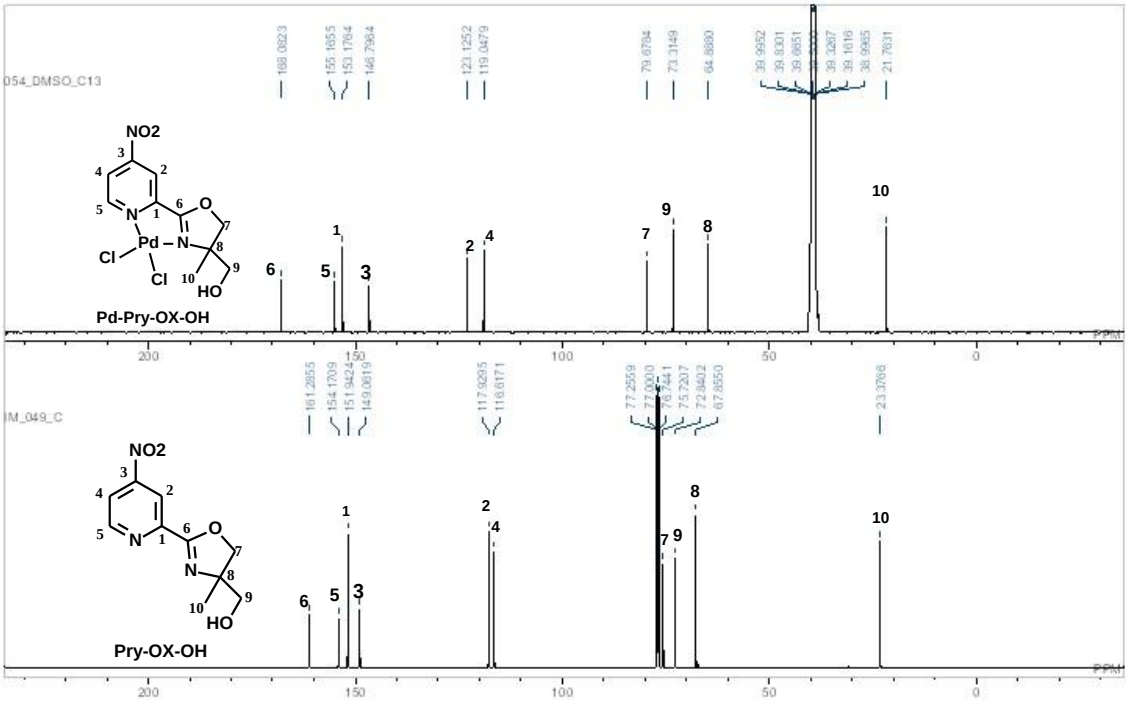


Figure 41: The ^{13}C NMR spectra of the Pyr-OX-OH ligand (above) and the corresponding Pd-Pyr-(OX-OH) (below) complex

The formation of Pd-Pyr-(OX-OH) from Pyr-OX-OH was further justified using the FTIR data for both the ligand and the complex. The shift in the position of vibration frequency band of *C=N* from 1630 cm^{-1} in the spectrum of OX-Pyr-OH ligand to 1606 cm^{-1} in the spectrum of Pd-Pyr-OX-OH is another indication that the ligand has been coordinated to the palladium center (Figure 42).

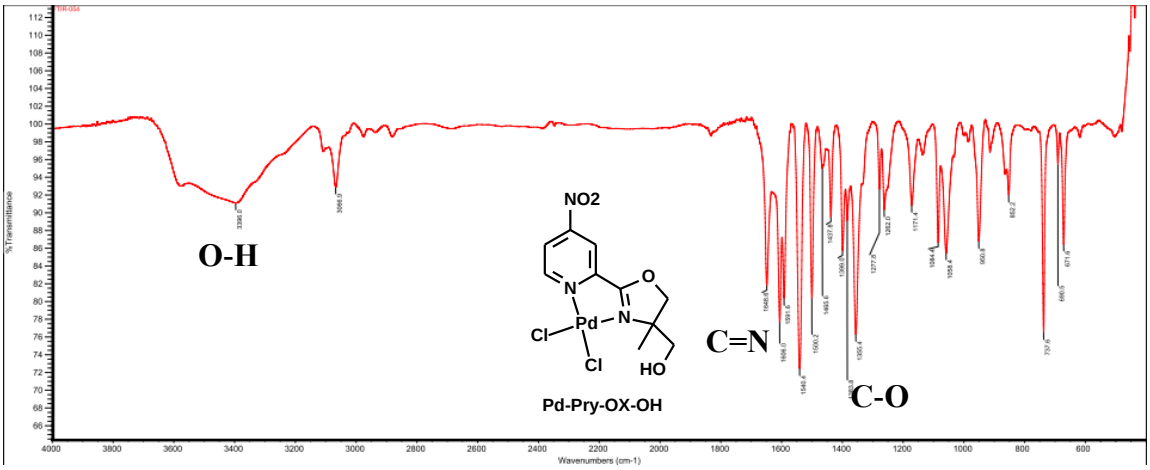


Figure 42: The FTIR spectra of the Pd-Pyr-(OX-OH) complex

2.4.3 Characterization of nickel(II)-BOX-OH complexes

The nickel-bis(hydroxymethyloxazoline) complexes, Ni-BOX-A and Ni-(BOX-OH)-1, were prepared from the reactions of BOX-A with nickel acetate tetrahydrate and BOX-OH-1 with nickel perchlorate hexahydrate respectively (Figure 21).

2.4.3.1 [1,2-bis (4,4-methyl-2-oxazolinyl)benzene] acetato nickel(II) complex (Ni-BOX-A)

The nickel complex Ni-BOX-A was prepared from the reaction of BOX-A with nickel(II) acetate tetrahydrate. The complex was purified by recrystallization from dichloromethane layered with diethyl ether. It was obtained in the form of green air stable powder. FTIR data of both the ligand and the complex was used to rationalize the formation of the complex from BOX-A ligand and $Ni(OAc)_2.4H_2O$ by identifying the shift in the vibration bands of some bonds, especially the ones attached to the atoms involved in the

coordination. The shift in the position of *C=N* band from 1662 cm^{-1} in the spectrum of BOX-A ligand to 1639 cm^{-1} in the spectrum of the complex Ni-BOX-A is an indication that the ligand was successfully coordinated to the nickel (Figure 43).

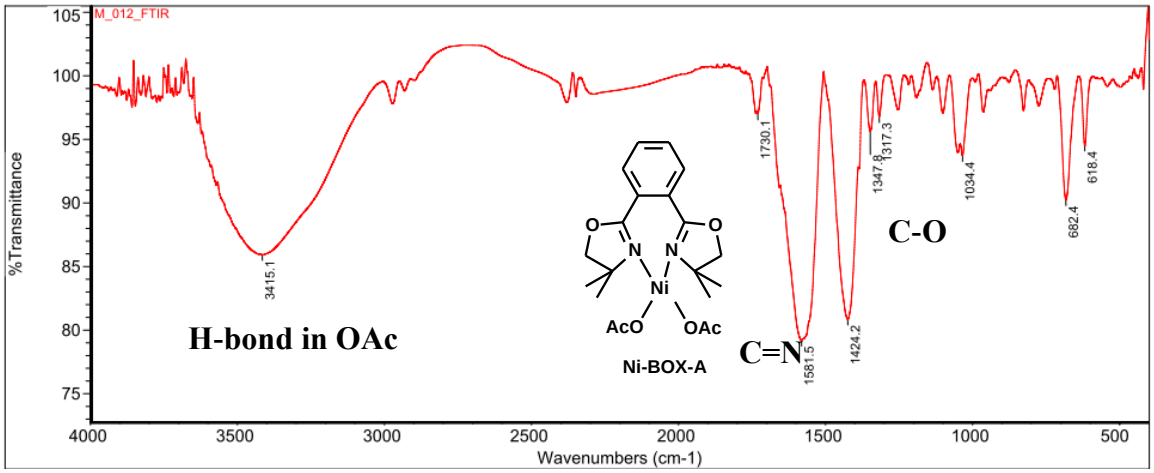


Figure 43: The FTIR spectrum of the Ni-BOX-A ligand

Furthermore, the elemental analysis of the complex was found to be consistent with the calculated mass percentage.

2.4.3.2 [1,2-bis(4-hydroxymethyl-4-methyl-2-oxazolinyl)benzene]perchlorato nickel(II) complex [Ni-(BOX-OH)-1]

The nickel complex Ni-(BOX-OH)-1 was prepared from the reaction of BOX-OH-1 with nickel(II) perchlorate hexahydrate. The complex was obtained in form of green air stable powder. To confirm the coordination of the BOX-OH-1 ligand to the Ni(II) ion, FTIR data both the ligand and the complex, and the vibration bands of important bonds on the ligand and complex were assigned and compared . The shift in the position of *C=N* band

from 1661 cm^{-1} in the spectrum of BOX-OH-1 ligand to 1639 cm^{-1} in the spectrum of the complex Ni-(BOX-OH)-1 is an indication that the ligand is coordinated to the nickel ion (Figure 44). Also, this was supported by the results of the elemental analysis obtained for this complex.

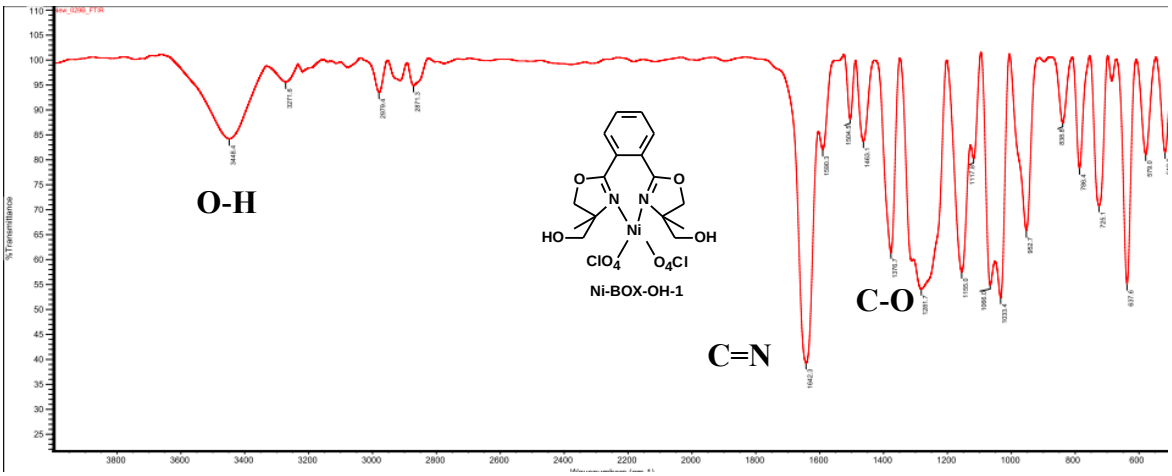


Figure 44: The FTIR spectrum of the Ni-BOX-OH-1 ligand

CHAPTER 3

PALLADIUM(II)-BOX-OH CATALYZED CROSS-COUPLING REACTIONS

Cross-coupling reactions, which are among the many other reactions catalyzed by palladium complexes, have become very powerful and important tool for making new C-C bonds. Generally, less-reactive organic electrophiles are involved in bond formation with several aryl halides and different kinds of carbon nucleophiles with the catalytic assistance of palladium catalysts [51]. The C-C coupling reactions are among the most rated reactions in organic synthesis, where many catalytic systems have been designed to carry out such conversions.

3.1 Experimental

All the chemicals and materials used to carry out these coupling reactions were of high purity as they were all used as purchased from the respective chemical companies. All the solvents employed for the reactions were in their anhydrous forms or freshly distilled. A GC instrument with FID detector was used to analyze the products of the coupling reactions. For the products that were obtained as a mixture, further purification was required by using a flash column chromatography with 60F Silica gel from Fluka Chemie AG (Buchs, Switzerland).

3.1.1 General procedure for palladium bis(oxazoline) catalyzed Suzuki-Miyaura coupling reactions

A palladium-bis(hydroxymethyloxazoline) complex (0.20 mol%, 0.0020 mmol), an aryl halide (1.0 mmol), an aryl boronic acid (1.5 mmol), potassium carbonate (2.0 mmol), dimethyl formamide (4.0 mL) and distilled water (4.0 mL) were charged into a round bottom 25 mL flask. The reaction mixture was stirred at ambient temperature. The progress of the reaction was monitored basically with the help of the gas chromatography technique. After the reaction time elapses or the reaction gets to completion, the product was extracted 3 times with 5 mL of ethyl acetate (3 x 5 mL). The combined organic phase extract was dried using anhydrous $MgSO_4$ to remove all possible moisture. The rotary evaporator was then used to remove the solvent under reduced pressure. The product was further purified by employing hexane-EtOAc (8:2) as an eluent solvent system in silica gel column chromatography.

The characterization data of the compounds were in entire agreement with work previously reported in literature [30, 63, 159-162].

3.1.2 General procedure for palladium bis(oxazoline) catalyzed Mizoroki-Heck coupling reactions

A palladium-bis(hydroxymethyloxazoline) complex (0.010 mmol), an aryl halide (1.0 mmol), a styrene derivative (1.5 mmol), KOH (2.0 mmol), DMF (3.0 mL) and distilled water (1.0 mL) were charged into a round bottom 25 mL flask fitted with a condenser. The reaction mixture was stirred at 90 ^{o}C. The progress of the reaction was monitored with the help of the gas chromatography technique. After the reaction time elapses or the

reaction gets to completion, the product was extracted 3 times with 5 mL of ethyl acetate (3 x 5 mL). The combined organic phase extract was dried using anhydrous $MgSO_4$ to remove all possible moisture traces. The rotary evaporator was then used to remove the solvent under reduced pressure. The product was further purified by employing hexane-EtOAc (7:3) as an eluent solvent system in silica gel column chromatography.

The characterization data results of the compounds were in entire agreement with work previously reported in literature [30, 159].

3.1.3 General procedure for palladium bis(oxazoline) catalyzed Sonogashira coupling reactions

In a round bottom 10 mL flask, a palladium-bis(hydroxymethyloxazoline) complex (0.010 mmol) was dissolved in acetonitrile (2 mL). An aryl halide (1.0 mmol), an alkyne (1.2 mmol), KOH (2.00 mmol) and distilled water (2 mL) were added to the round bottom 10 mL flask. The mixture was stirred at ambient temperature (or 60 ^oC) for the required time 2-6 h. After the reaction time elapses or the reaction gets to completion, the product was extracted 3 times with 5 mL of ethyl acetate (3 x 5 mL). The combined organic phase extract was dried using anhydrous $MgSO_4$ to remove all possible moisture traces. The rotary evaporator was then used to remove the solvent under reduced pressure. The products were analyzed using GC instrument, and were then purified by employing hexane-ethyl acetate as an eluent solvent system in silica gel column chromatography. The characterization data were in entire agreement with the previously reported literature [38, 62, 163-168].

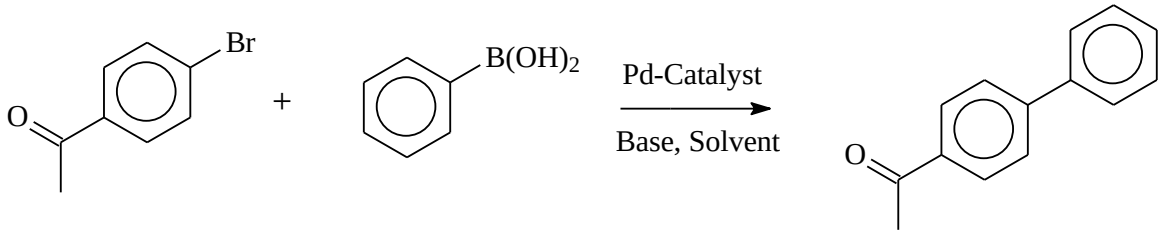
3.2 Results and Discussions

3.2.1 Suzuki-Miyaura Coupling Reaction

The Suzuki-Miyaura coupling reaction of phenylboronic acid with 4-bromoacetophenone was carried out using the newly developed palladium catalysts (Pd-(BOX-OH)-1 and Pd-(BOX-OH)-2) and some commercially available palladium complexes for the purpose of comparison under some specific experimental conditions. The Pd-BOX catalysts have both air and moisture stability that give them pronounced advantages over palladium phosphine catalysts in terms of tolerance to substrates, temperature conditions, time of reaction and overall the catalytic activity [169]. The results of the optimization of the reaction conditions and catalytic activities of these catalysts are presented in Table 4. Pd-(BOX-OH)-1 showed high activity when the reaction was carried out in DMF-H_2O mixed solvent in a ratio of 1:1 at room temperature for 30 minutes giving a yield of 96% (Table 4, entry 5). Interestingly, when neat water was employed at 50 °C for 1 hour, the new palladium catalysts, Pd-(BOX-OH)-1 and Pd-(BOX-OH)-2 , exhibited remarkable catalytic activities leading to excellent isolated yields (97% and 98%) (Table 4, entries 6 and 11, respectively). The activity of Pd-(BOX-OH)-1 and Pd-(BOX-OH)-2 were higher than most of the tested commercial palladium complexes. For instance, $PdCl_2$ and $Pd(PPh_3)_4$ gave very good isolated yields (87% and 73%, respectively) (Table 4, entries 14 and 16) in neat water. Lower yields of coupling product (64%) were observed with $Pd(OAc)_2$ and $PdCl_2$-biPy (Table 4, entries 13 and 17), while only traces of coupling product were detected with $PdCl_2$Phen as a catalyst (Table 4, entry 18). BOX ligands are now well defined for their appreciable performance that they demonstrated as compared to other dinitrogen ligands, including 10-phenanthroline, 2,2′-bipyridine, and pyridine

triazole [170]. The activity of a palladium complex Pd-BOX-A, which has a similar structure to Pd-BOX-OH but differs by the absence of hydroxyl groups, gave lower yield of coupling product (43%) in neat water (Table 4, entry 12). The high activity of the new catalysts Pd-(BOX-OH)-1 and Pd-(BOX-OH)-2 in neat water could be attributed to the presence of the hydroxyl group which contribute to the solubility of the catalysts in water as a reaction medium as compared to other commercial palladium complexes, and hence, increase their catalytic activity.

Table 4: Suzuki-Miyaura coupling reaction using phenylboronic acid and 4-bromoacetophenone: Optimization of reaction conditions.[a]

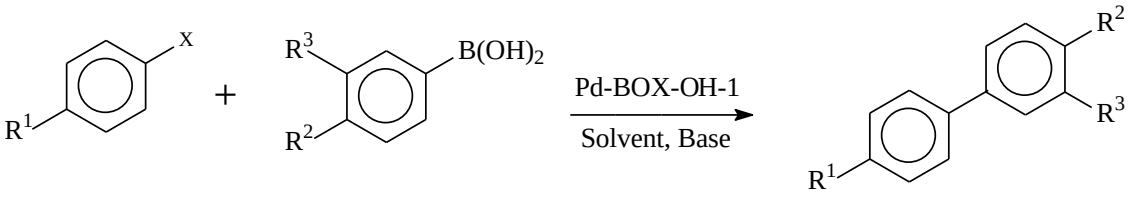


Entry	Pd-Catalyst	Solvent	Base	Time (h)	T (°C)	Yield (%)[b]
1	Pd-(BOX-OH)-1	Neat H_2O	K_2CO_3	1	RT	41
2	Pd-(BOX-OH)-1	Neat DMF	K_2CO_3	1	RT	38
3	Pd-(BOX-OH)-1	Neat MeOH	K_2CO_3	1	RT	7
4	Pd-(BOX-OH)-1	H_2O-DMF (1:1)	K_2CO_3	1	RT	98
5	Pd-(BOX-OH)-1	H_2O-DMF (1:1)	K_2CO_3	0.5	RT	96
6	Pd-(BOX-OH)-1	Neat H_2O	K_2CO_3	1	50	97
7	Pd-(BOX-OH)-1	Neat H_2O	K_2CO_3	1	45	92
8	Pd-(BOX-OH)-1	Neat H_2O	Et_3N	1	50	53
9	Pd-(BOX-OH)-1	Neat H_2O	KOH	1	50	69
10	Pd-(BOX-OH)-1	Neat H_2O	Nil	1	50	Traces
11	Pd-(BOX-OH)-2	Neat H_2O	K_2CO_3	1	50	98
12	Pd-BOX-A	Neat H_2O	K_2CO_3	1	50	43
13	$Pd(OAc)_2$	Neat H_2O	K_2CO_3	1	50	64
14	$PdCl_2$	Neat H_2O	K_2CO_3	1	50	87
15	$Pd(PPh_3)_2Cl_2$	Neat H_2O	K_2CO_3	1	50	15
16	$Pd(PPh_3)_4$	Neat H_2O	K_2CO_3	1	50	73
17	$PdCl_2$-2,2'-bipyridine	Neat H_2O	K_2CO_3	1	50	64
18	$PdCl_2$-1,10-phenanthroline	Neat H_2O	K_2CO_3	1	50	Traces

[a] Reaction Conditions: [Pd] (0.0020 mmol), 4-bromoacetophenone (1.00 mmol), phenylboronic acid (1.20 mmol), base (2.00 mmol), solvent (8.0 mL).
[b] Isolated Yield.

The Suzuki-Miyaura coupling reaction of various aryl boronic acids with aryl halides using the newly developed palladium catalyst, Pd-(BOX-OH)-1, were carried out in neat water under the stated experimental conditions. The results are given in Table 5. In 2011, phosphine palladium complex was used to conduct Suzuki coupling reactions employing Na_2CO_3 as a base in neat water and the reaction was carried out under air and at room temperature, however, these reactions take considerable reaction time and gave lower yields [63]. The aryl bromide with an electron releasing group (Table 5**,** entry 7) was less reactive (83%) than the aryl bromides with electron withdrawing substituents (Table 5**,** entries 6 and 8), which gave excellent yields of coupling products (98 and 94%). Also, the aryl iodides showed similar trend, however, the hydroxyl substituted substrates (aryl iodides and aryl boronic acids) displayed an improved activity, perhaps due to the ability of these substrates to solubilize in the aqueous reaction medium. Also, according to the literature, the aromatic spacer and the oxazoline rings help in inducing the electronic effects of the palladium center by the synergistic σ-donor ability of the ligand as reported in similar ligands like imidazolinylidene [171]. Although the substituents on the oxazoline rings give rise to the steric effects, they offer some kinetic stability to the intermediate complex, which promotes a successful reductive elimination [172].

Table 5: Pd-(BOX-OH)-1 complex employed as catalyst in Suzuki-Miyaura coupling reaction in aqueous medium of various phenylboronic acids with different aryl halides.[a]



Entry	R^1	X	R^2, R^3	Yield (%)[b]
1	H	I	H, H	92
2	H	I	OCH_2O	95
3	*p*-OCH_3	I	H, H	90
4	*p*-OH	I	H, OCH_2CH_3	93
5	*p*-OH	I	H, OH	94
6	*p*-C=O(CH_3)	Br	H, H	98
7	*p*-OCH_3	Br	H, H	83
8	*p*-CHO	Br	H, H	94

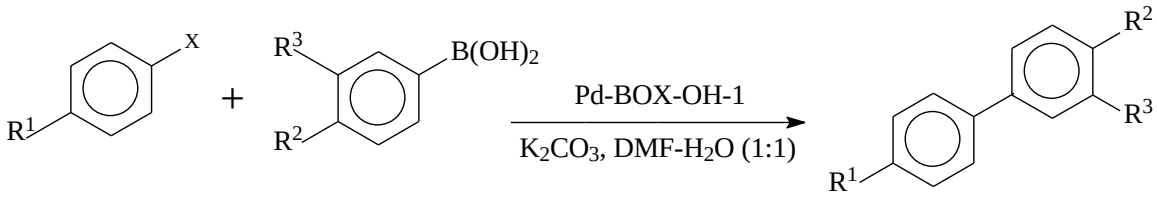
[a] Reaction Conditions: Pd-(BOX-OH)-1 (0.050 mmol), arylboronic acid (1.50 mmol), aryl halide (1.00 mmol), K_2CO_3 (2.00 mmol), H_2O (8.0 mL), 50 °C, 1h.
[b] Isolated Yield.

We have also adopted the optimized conditions of the Suzuki-Miyaura coupling reactions that were obtained using our Pd-(BOX-OH)-1 as a catalyst in DMF-H_2O (1:1) and using K_2CO_3 at room temperature (Table 4, entry 5).

Various aryl halides (iodide, bromide and chloride) with different aryl boronic acids were reacted under the optimized conditions (Table 6). The reactions of various aryl iodides with different aryl boronic acids gave excellent yields (88-98%) of coupling products at room temperature and in 30 minutes (Table 6, entries 1-9). Similarly, the reactions of aryl

bromides with various aryl boronic acids (Table 6, entries 10-16) were also very successful. The coupling reactions of chlorobenzene with two different substituted aryl boronic acids were conducted at an elevated temperature (110 ^{o}C) for longer reaction time (12 h) to give also high isolated yields of products (88-89%) (Table 6, entries 17 and 18). The reactions of 4-iodoacetophenone and 4-bromoacetophenone with phenylboronic acid under the same conditions gave similarly high isolated yields (99% and 96%, respectively) (Table 6, entries 8 and 12). Also, the reactions of 4-ethoxyphenyl boronic acid with 4-iodoacetophenone and with 4-bromoacetophenone under the same conditions gave also excellent yields of coupling products (98% and 96%, respectively) (Table 6, entries 9 and 13). Moreover, the reactions of 4-bromoanisole and 4-iodoanisole with phenyboronic acid led to coupling products in high yields (88% and 92%) (entries 5 and 14). The aryl chlorides (chlorobenzene) were compared with the aryl iodide (iodobenzene) through their respective reactions with 3,4-(methylenedioxy)-phenylboronic acid and 4-ethoxyphenyl boronic acid (Table 6, entries 2 and 18, 3 and 17, respectively). The coupling reactions of chlorobenzene gave very high yields (88% and 89%) with 3,4-(methylenedioxy)phenylboronic acid and 4-ethoxyphenylboronic acid, respectively, but at a higher temperature (110 ^{o}C) and for a longer reaction time 12 h. Iodobenzene reacted at room temperature to give high isolated yields (98% and 97%) of coupling products with the same phenylboronic acid substrates. Hence, it can be depicted from Table 6 that aryl iodides are more reactive in Suzuki-Miyaura coupling reaction than aryl bromides, and aryl chlorides are the least reactive under similar reaction conditions.

Table 6: Suzuki-Miyaura coupling reaction of various aryl halides with different arylboronic acids using Pd-(BOX-OH)-1 as a catalyst.[a]



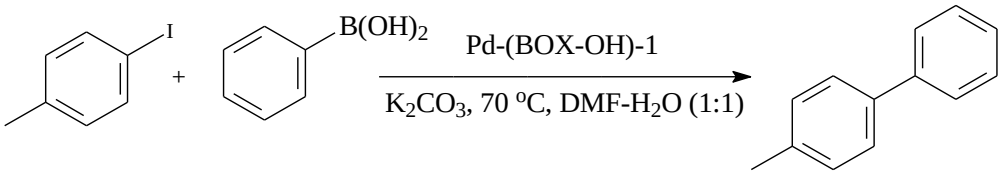
Entry	R^1	R^2	R^3	X	Time (h)	Yield (%)[b]
1	H	H	H	I	0.5	96
2	H	OCH_2O		I	0.5	98
3	H	H	OCH_2CH_3	I	0.5	97
4	H	H	OH	I	1.0	90
5	OCH_3	H	H	I	1.0	92
6	OH	H	OCH_2CH_3	I	1.0	94
7	OH	H	OH	I	1.0	88
8	$COOCH_3$	H	H	I	0.5	99
9	$COOCH_3$	H	OCH_2CH_3	I	0.5	98
10	$(CH_3)C=O$	H	H	Br	1.0	99
11	$(CH_3)C=O$	H	OH	Br	0.5	97
12	$COOCH_3$	H	H	Br	0.5	96
13	$COOCH_3$	H	OCH_2CH_3	Br	0.5	96
14	OCH_3	H	H	Br	1.0	88
15	HC=O	H	H	Br	0.5	99
16	HC=O	H	OCH_2CH_3	Br	0.5	99
17[c]	H	H	OCH_2CH_3	Cl	12	88
18[c]	H	OCH_2O		Cl	12	89

[a] Reaction Conditions: Pd-(BOX-OH)-1 (0.050 mmol), aryl boronic acid (1.5 mmol), aryl halide (1.0 mmol), K_2CO_3 (2.0 mmol), DMF (4.0 mL), H_2O (4.0 mL), R.T.
[b] Isolated Yield.
[c] 110 ^oC

3.2.1.1 The recyclability of Pd-(BOX-OH)-1 in Suzuki–Miyaura coupling reaction

Remarkable activity, high selectivity and low catalyst loading are the major advantages of the homogeneous catalysis; hence, it is widely employed for various transformations. Nonetheless, separating the product from the catalyst is considered as the main challenge associated with this process. This narrows the chance of reusing catalysts, and hence, increasing the overall cost of the production process [173]. Nowadays, chemical and pharmaceutical industries are looking for the catalysts that can be easily recycled. Pd-(BOX-OH)-1 in DMF–H_2O with ratio 1:1 was used to investigated the recycling ability of the homogeneous catalytic system in the Suzuki–Miyaura coupling reaction of 4-iodotoluene with phenylboronic acid at 70 °C for 1 h. The results of the recycling experiments obtained are presented in Figure 45. After the first cycle of the coupling reaction, 5.0 ml of n-hexane was used to extract the product four times (4 × 5.0 mL). The remaining DMF–H_2O phase was charged with fresh substrates (4-iodotoluene with phenylboronic acid) and a base (Figure 45). The coupling reaction was carried out repeatedly under the same experimental conditions. Remarkably, the catalytic system was able to be recycled up to 6 times without showing any loss in the catalytic activity. However, it is important to point out that this high recycling ability of the catalytic system is limited only to non-polar products and can easily be separated from the reaction mixture by extraction simply by using a non-polar solvent (n-hexane) without any loss of the catalyst (Pd-(BOX-OH)-1) from the DMF–H_2O phase. The turnover frequency of Pd-BOX-1 is estimated for the 6 cycles as 1500 h^{-1}. In order to confirm the efficiency of the Pd-(BOX-OH)-1 catalyst, an experiment with a ratio of 4-iodotoluene (4.0 mmol) to Pd-(BOX-OH)-1 catalyst (0.002 mmol) equal to 2000 for 1 h was successfully carried

out leading to a complete conversion of the 4-iodotoluene, and an excellent isolated yield of the product (98%).



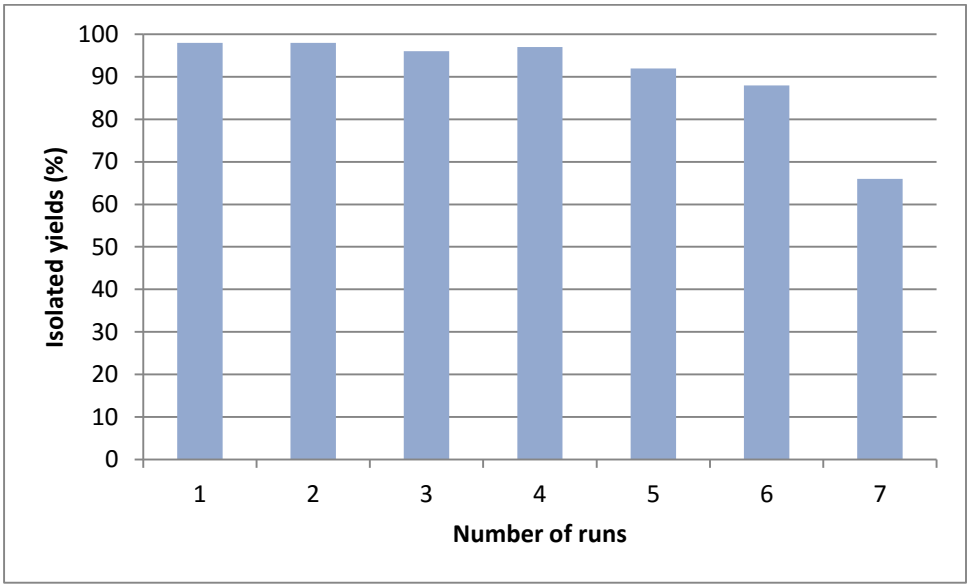


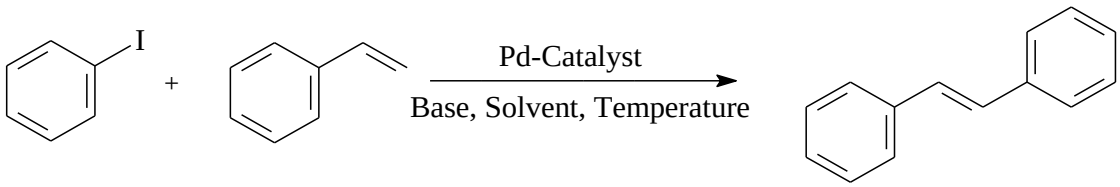
Figure 45: Recycling of Pd-(BOX-OH)-1 catalyst in Suzuki–Miyaura coupling reaction of 4-iodotoluene with phenylboronic acid

3.2.2 Mizoroki-Heck coupling reaction

The optimization of Mizoroki-Heck coupling reactions was realized using iodobenzene and phenylacetylene as model substrates and in the presence of Pd-(BOX-OH)-1 as a catalyst. The results obtained are summarized on **(**Table 7). A comparative study of the catalytic activity of Pd-(BOX-OH)-1 with some commercially available catalysts under the optimized reaction conditions were also accomplished (Table 7, entries 14-18). The reactions of iodobenzene with phenylacetylene catalyzed by Pd-(BOX-OH)-1 in neat DMF or neat water, employing KOH as a base (Table 7, entries 4 and 5) gave moderate

yields (51% and 46%, respectively). However, the use of a mixed solvent (H_2O and DMF in a ratio of 1:1) has improved the significantly yield to 89% with K_2CO_3, to 67% with Et_3N, and to 90% with KOH as a base (Table 7, entries 1-3). The increase in the H_2O to DMF ratio to (1:3) has enhanced further the yields of the coupling product to 94% with K_2CO_3, to 73% with Et_3N, and to 96% with KOH as a base (Table 7, entries 7-9). We have observed a close correlation between the catalytic activity and the type of base in the coupling reaction; KOH was the most suitable base, followed by the K_2CO_3, while Et_3N was found to give lower yields of the coupling products. Hence, we have adopted KOH as the most suitable base of choice in the subsequent study. Moreover, we have further conducted the screening of the reaction conditions by using the mixed H_2O and CH_3CN solvent system in three different ratios, employing KOH as a base: with H_2O:CH_3CN ratio of 1:1, the coupling reaction gave a very good yield (76%) of product (Table 7, entry 10), and a moderate yield (50%) (Table 7, entry 11) with a ratio of 3:1, while the highest yield (90%) was obtained with H_2O:CH_3CN ratio of 1:3 (Table 7, entry 12). Overall, the optimum reaction conditions for Mizoroki-Heck coupling reaction catalyzed by Pd-(BOX-OH)-1 were found with KOH as a base and H_2O-DMF (1:3) as a solvent system at 90 °C (Table 7, entry 7). Under these optimized conditions, some commercially available catalysts were tested (Table 7, entries 14-18). $Pd(PPh_3)_2Cl_2$ gave a good yield (80%) of coupling product (Table 7, entry 16) and $PdCl_2$-1,10-phenanthroline gave 56% only (Table 7, entry 18). $Pd(OAc)_2$, $Pd(PhCN)_2Cl_2$ and $PdCl_2$-2,2'-bipyridine gave moderate yields of products (60%, 62% and 70%, respectively) (Table 7, entries 14, 15 and 17). Pd-(BOX-OH)-1 catalyst showed the highest catalytic activity as compared to the commercially available catalysts (Table 7, entry 7).

Table 7: Mizoroki-Heck coupling reaction of iodobenzene with styrene: Optimization of the reaction conditions.[a]



Entry	Pd-Catalyst	Solvent	Base	Yield (%)[b]
1	Pd-(BOX-OH)-1	H_2O-DMF (1:1)	K_2CO_3	89
2	Pd-(BOX-OH)-1	H_2O-DMF (1:1)	Et_3N	67
3	Pd-(BOX-OH)-1	H_2O-DMF (1:1)	KOH	90
4	Pd-(BOX-OH)-1	Neat DMF	KOH	51
5	Pd-(BOX-OH)-1	Neat H_2O	KOH	46
6	Pd-(BOX-OH)-1	H_2O-DMF (3:1)	KOH	51
7	Pd-(BOX-OH)-1	H_2O-DMF (1:3)	KOH	96
8	Pd-(BOX-OH)-1	H_2O-DMF (1:3)	Et_3N	73
9	Pd-(BOX-OH)-1	H_2O-DMF (1:3)	K_2CO_3	94
10	Pd-(BOX-OH)-1	H_2O-CH_3CN (1:1)	KOH	76
11	Pd-(BOX-OH)-1	H_2O-CH_3CN (3:1)	KOH	50
12	Pd-(BOX-OH)-1	H_2O-CH_3CN (1:3)	KOH	92
13	Pd-(BOX-OH)-1	Neat CH_3CN	KOH	55
14	$Pd(OAc)_2$	H_2O-DMF (1:3)	KOH	60
15	$Pd(PhCN)_2Cl_2$	H_2O-DMF (1:3)	KOH	62
16	$Pd(PPh_3)_2Cl_2$	H_2O-DMF (1:3)	KOH	80
17	$PdCl_2$-2,2'-bipyridine	H_2O-DMF (1:3)	KOH	70
18	$PdCl_2$-1,10-phenanthroline	H_2O-DMF (1:3)	KOH	56

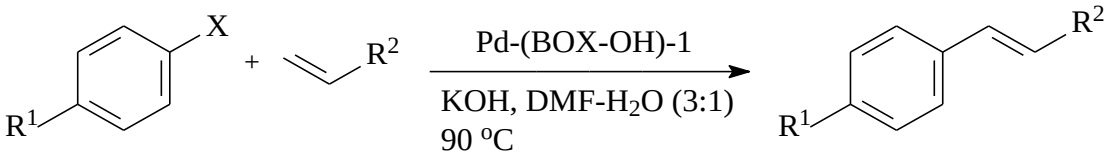
[a] Reaction Conditions: [Pd] (0.010 mmol), aryl iodide (1.0 mmol), alkene (1.2 mmol), base (2.0 mmol), Solvent (4.0 mL), 3 h, 90 °C.

[b] Isolated yield.

Mizoroki-Heck coupling reaction of various aryl halides with different alkenes were studied using the optimized experimental conditions. The reactions were formerly conducted in the presence of aminooxazolines as ligands [74, 174]. Nevertheless, there reactions required considerably elevated temperature (>140 °C) and significantly lengthy reaction time (around two days) in order to obtain noticeable conversions. More recently, a new palladium catalyst (Pd-BOX-1), which was developed in our laboratory, was found to be highly efficient in Mizoroki-Heck coupling reactions [62]. In this study, Pd-(BOX-OH)-1 was used as the catalyst in DMF-H_2O (3-1 mL) for 3 h at 90 ^oC (Table 8). Interestingly, the reactions of 1,4-diiodobenzene with styrene and 4-methoxystyrene gave excellent isolated yields of the coupling products (Table 8, entries 3 and 4). Excellent yields were obtained for the reactions of iodobenzene with various styrene derivatives (Table 8, entries 1-2 and 7-9). The reactions of styrene and allyl benzene with iodobenzene gave excellent yields of products (92 % and 95 %, respectively) (Table 8, entries 1 and 2). Moreover, excellent yields (82-94 %) for the reactions of styrene with 2,4,6-trimethylstyrene, 2,6-dichlorostyrene and m-nitrostyrene were achieved (Table 8, entries 7-9). The aryl bromides, as expected, were less reactive and the reaction required a higher temperature (100 ^oC) and a longer reaction time (6 h) to give the excellent yield of the isolated product (29 %) (Table 8, entry 10). Allyl chloride, acrylonitrile and methylacrylate were also employed in this study (Table 8, entries 11-13). The results of the coupling reactions of these three substrates with iodobenzene were recorded; the coupling reactions of iodobenzene with acrylonitrile or methylacrylate gave excellent yields of the isolated products (92 % and 90 %, respectively) (Table 8, entries 11 and 12),

and only a moderate yield (48 %) of the coupling product was isolated with the reaction of allyl chloride and iodobenzene (Table 8, entry 13).

Table 8: Mizoroki-Heck coupling reactions of aryl halides with alkenes catalyzed by Pd-(BOX-OH)-1.[a]



Entry	R^1	X	R^2	Yield (%)[b]
1	H	I	C_6H_5	95
2	H	I	$C_6H_5CH_2$	92
3	I	I	C_6H_5	94
4	I	I	*p*-OCH_3-C_6H_4	91
5	NO_2	I	C_6H_5	80
6	$CH_3(C=O)$	I	C_6H_5	96
7	H	I	2,4,6-trimethyl-C_6H_4	94
8	H	I	2,6-dichloro-C_6H_4	90
9	H	I	*m*-NO_2-C_6H_4	82
10[c]	$CH_3(C=O)$	Br	C_6H_5	29
11	H	I	$COOCH_3$	90
12	H	I	CN	92
13	H	I	CH_2Cl	48

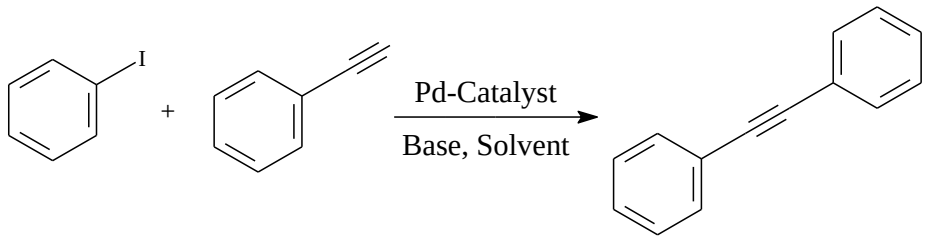
[a] Reaction conditions: Pd-(BOX-OH)-1 (0.010 mmol), aryl iodide (1.0 mmol), alkene (1.2 mmol), KOH (2.0 mmol), DMF:H_2O (3:1 mL), 3 h, 90 °C.
[b] Isolated yield.
[c] 100 °C, 6 h.

3.2.3 Sonogashira coupling reactions

Sonogashira reaction was conducted using the newly developed Pd-(BOX-OH)-1 complex and the experimental reaction conditions were optimized. Table 9 summarizes the optimization of the reaction conditions for Sonogashira coupling reactions using iodobenzene and phenylacetylene as model substrates. It was observed that the reaction did not work well at room temperature under the various reaction conditions of solvents and bases. Thus, no products were formed for all conducted reactions for 1 h (Table 9, entries 1-6). However, when the reactions were allowed to run for longer time (6 h) using H_2O and DMF (1:1) and in the presence of various bases, it was noticed that reasonable yields of coupling products were obtained (71%, 68% and 66%) (Table 9, entries 7-9). Furthermore, improved results were observed when the solvent system was changed to CH_3CN and H_2O (1:1) for 3 h and with KOH, K_2CO_3 and Et_3N as base; the yields of the products were 65%, 68% and 58%, respectively (Table 9, entries 10-12). The reactions in neat DMF showed moderate reactivity in 3 h and hence fairly moderate yields (39-54%) were obtained. KOH appears to be the most suitable base for the Sonogashira reactions under the stated reaction conditions in the presence of Pd-(BOX-OH)-1 as a catalyst and gave the highest yield (54%) (Table 9, entry 13), Et_3N produced a yield of 39% (entry 15), and a yield of 50% was obtained with K_2CO_3 (Table 9, entry 14). The catalytic activity of the Pd-(BOX-OH)-1 complex has significantly improved when the temperature was elevated to 60°C; the coupling reactions were completed in 30 minutes (Table 9, entries 16-21). Although different bases and solvent systems were tested again at 60 ^oC, the most suitable solvent system was H_2O and CH_3CN in (1:1) ratio and KOH as a suitable base, where the best yield of the coupling product was obtained (98%)

(Table 9, entry 16). We have applyied the optimized experimental conditions at 60 ^{o}C to Sonogashira coupling reactions catalyzed by other palladium(II) complexes that were commercially available; $PdCl_2$-bipy, $Pd(PPh_3)_2Cl_2$ and $PdCl_2$-Phen gave relatively lower yields of 84%, 89%, 67%, respectively (Table 9, entries 22-24) as compared to Pd-(BOX-OH)-1 . Hence, the newly developed Pd-(BOX-OH)-1 has an excellent catalytic activity in Sonogashira coupling reactions under the stated reaction conditions.

Table 9: Sonogashira coupling reaction of iodobenzene and phenylacetylene: Optimization of reaction conditions.[a]



Entry	Pd-Catalyst	Solvent	Base	Time (h)	T (^{o}C)	Yield (%)[b]
1	Pd-(BOX-OH)-1	H_2O-CH_3CN (1:1)	KOH	1.0	RT	-
2	Pd-(BOX-OH)-1	H_2O-CH_3CN (1:1)	K_2CO_3	1.0	RT	-
3	Pd-(BOX-OH)-1	H_2O-CH_3CN (1:1)	Et_3N	1.0	RT	-
4	Pd-(BOX-OH)-1	H_2O-DMF (1:1)	KOH	1.0	RT	-
5	Pd-(BOX-OH)-1	H_2O-DMF (1:1)	K_2CO_3	1.0	RT	-
6	Pd-(BOX-OH)-1	H_2O-DMF (1:1)	Et_3N	1.0	RT	-
7	Pd-(BOX-OH)-1	H_2O-DMF (1:1)	KOH	6.0	RT	71
8	Pd-(BOX-OH)-1	H_2O-DMF (1:1)	K_2CO_3	6.0	RT	68
9	Pd-(BOX-OH)-1	H_2O-DMF (1:1)	Et_3N	6.0	RT	66
10	Pd-(BOX-OH)-2	H_2O-CH_3CN (1:1)	KOH	3.0	RT	68
11	Pd-(BOX-OH)-2	H_2O-CH_3CN (1:1)	K_2CO_3	3.0	RT	65
12	Pd-(BOX-OH)-2	H_2O-CH_3CN (1:1)	Et_3N	3.0	RT	58

13	Pd-(BOX-OH)-1	Neat DMF	KOH	3.0	RT	54
14	Pd-(BOX-OH)-1	Neat DMF	K_2CO_3	3.0	RT	50
15	Pd-(BOX-OH)-1	Neat DMF	Et_3N	3.0	RT	39
16	Pd-(BOX-OH)-1	H_2O-CH_3CN (1:1)	KOH	0.5	60	98
17	Pd-(BOX-OH)-1	H_2O-CH_3CN (1:1)	K_2CO_3	0.5	60	92
18	Pd-(BOX-OH)-1	H_2O-CH_3CN (1:1)	Et_3N	0.5	60	71
19	Pd-(BOX-OH)-1	H_2O-DMF (1:1)	KOH	0.5	60	92
20	Pd-(BOX-OH)-1	H_2O-DMF (1:1)	K_2CO_3	0.5	60	89
21	Pd-(BOX-OH)-1	H_2O-DMF (1:1)	Et_3N	0.5	60	80
22	$PdCl_2$-bipy	H_2O-CH_3CN (1:1)	KOH	0.5	60	84
23	$Pd(PPh_3)_2Cl_2$	H_2O-CH_3CN (1:1)	KOH	0.5	60	89
24	$PdCl_2$-Phen	H_2O-CH_3CN (1:1)	KOH	0.5	60	67

a Reaction Conditions: [Pd] (0.010 mmol), iodobenzene (1.0 mmol), phenylacetylene (1.5 mmol), base (2.0 mmol), solvent (4.0 ml).
b Isolated yield.

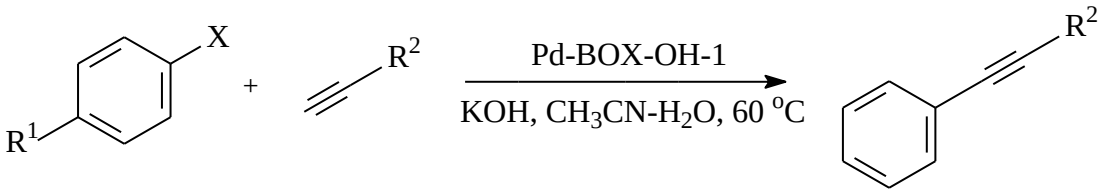
The Sonogashira coupling reactions of aryl halides with different alkynes and dialkynes were conducted under the following optimized reaction conditions: 60 °C, CH_3CN: H_2O (1:1), KOH as base, and 0.5 h. The results are summarized on Table 10. Various aryl iodides reacted with different alkynes in the presence of Pd-(BOX-OH)-1 as a catalyst. The coupling reactions between the aryl iodides and phenylacetylene were considered. Aryl iodides with electron releasing and electron withdrawing substituents (4-iodoacetophenone, 4-iodobenzoate, 4-iodobenzoic acid, 4-iodobenzaledhyde, 4-iodoanisole, and 4-iodophenol), were very reactive in the coupling reactions with phenyl acetylene. Excellent isolated yields (91%-98%) of coupling products were obtained (Table 10, entries 1-7). Furthermore, aryl bromides were also considered in Sonogashira coupling reactions with phenylacetylene, however, poor yields were obtained even after

24 h of reactions (Table 10, entries 8 and 9). Various alkyl alkynes and functionalized alkyl alkynes were also considered in the study (Table 10, entries 10-13). Higher yields (90% and 92%) of coupling products were obtained from the reaction of iodobenzene with functionalized alkynes such as 5-cyano-1-pentyne and 6-chloro-1-hexyne (Table 10, entries 12 and 13) as compared to the reactions of normal alkyl alkynes (80% and 89%) (Table 10, entries 10 and 11). Moreover, aryl and alkyl dialkynes were considered in this coupling process. The coupling reaction of iodobenzene with 1, 7-octadiyne was less efficient and gave a moderate yield (60%) (Table 10, entry 14). However, the coupling reaction of iodobenzene with 1,4-diethynylbenzene was very successful where the internal dialkyne was produced in excellent yield (98%) (Table 10, entry 15).

In summary, aryl iodides were found to be more reactive than aryl bromides under the same reaction conditions. Furthermore, the presence of electron withdrawing substituent in para on the aryl iodide increased its reactivity and the electron releasing substituents lower the rate of the coupling reaction. Also, it was observed that aryl alkynes were more reactive than the alkyl alkynes. In addition, the normal alky alkynes were less reactive than the functionalized alkyl alkynes.

These results clearly demonstrate a good catalytic activity of the Pd-(BOX-OH)-1 catalyst conditions in the Sonagashira coupling reactions comparable to those published on literature [62] under the optimized and higher than the other reported palladium-phosphine and palladium-nitrogen catalysts [87].

Table 10: Sonogashira coupling reactions of aryl iodides with alkynes catalyzed by Pd-(BOX-OH)-1.[a]



Entry	R^1	X	R^2	Time H	Yield (%)[b]
1	H	I	C_6H_5	0.5	98
2	$CH_3(C=O)$	I	C_6H_5	0.5	98
3	OCH_3	I	C_6H_5	0.5	91
4	H(C=O)	I	C_6H_5	0.5	97
5	$OCH_3(C=O)$	I	C_6H_5	0.5	98
6	OH(C=O)	I	C_6H_5	0.5	94
7	OH	I	C_6H_5	0.5	89
8	H(C=O)	Br	C_6H_5	24	28
9	$CH_3(C=O)$	Br	C_6H_5	24	21
10	H	I	$(CH_2)_3CH_3$	6	89
11	H	I	$(CH_2)_7CH_3$	12	80
12	H	I	$(CH_2)_3CN$	6	92
13	I	I	$(CH_2)_4Cl$	12	90
14	H	I	H—≡—$(CH_2)_4$	12	60
15	H	I	H—≡—C_6H_4	12	98

[a] Reaction Conditions: Pd-(BOX-OH)-1 (0.010 mmol), aryl halide (1.0 mmol) or aryl dihalide (0.50 mmol), alkyne (1.5 mmol) or dialkyne (0.75 mmol), KOH (2.0 mmol), CH_3CN:H_2O (1:1; 4 mL), 60 °C.

[b] Isolated yield.

CHAPTER 4

NICKEL(II)-(BOX-OH-1) CATALYZED C-H ARYLATION OF ARENES

4.1 General procedure for nickel C-H arylation of unactivated arenes coupling reactions.

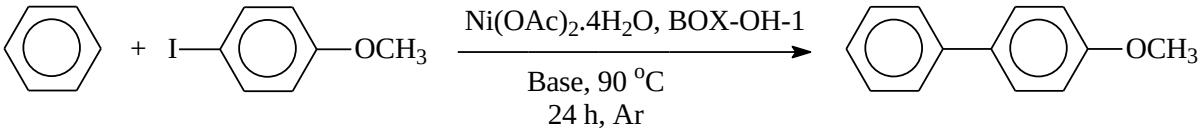
An aryl halide (0.50 mmol), a nickel complex, a ligand and a base were charged into a cylindrical 25 mL chlenk tube coupled with a vacuum line. The schlenk tube was flashed several times with an inert gas (argon), then 2 mL of an arene was added using cannula. The reaction mixture was stirred at 120 °C for 24 h and then allowed to cool to room temperature. Diethyl ether and water were used to dilute the reaction mixture and extract the product. Anhydrous sodium sulfate was used to remove all traces of moisture from the organic phase, which was then concentrated using a rotary evaporator. The residue was purified through silica gel column chromatography employing ethyl acetate and petroleum ether (8:2) mixture solvent system to afford the highly pure desired products.

4.2 Results and Discussions

We have carefully investigated the catalytic activity of the system formed from the novel BOX-OH-1 ligand and nickel precursors in C-H activation reactions of aryl halides and arenes. The reaction conditions were optimized by considering 4-iodoanisole and

benzene as model substrates under inert atmosphere using BOX-OH-1 and $Ni(OAc)_2.4H_2O$ precursor as the catalytic system. The effects of changing base and the type of nickel complex were also considered. The results are summarized on the Table 11. $NiCl_2.6H_2O$ was tested using K_2CO_3, LiH, Et_3N and K^tOBu as a base, however, no conversions were observed for K_2CO_3 and Et_3N (Table 11**,** entries 1 and 4), while LiH and K^tOBu gave low to moderate yields (10% and 43%, respectively) (Table 11**,** entries 2 and 3). $Ni(ClO_4)_2.6H_2O$ and $Ni(OTf)_2$ were also considered, but no tangible conversions were obtained with any of the bases mentioned above (Table 11**,** entries 11-16). Interestingly, $Ni(OAc)_2.4H_2O$ was observed to give a good yield of coupling product with LiH and a very good yield with K^tOBu (Table 11**,** entries 6 and 7). No product was recorded in the absence of BOX-OH-1 ligand (Table 11, entries 20). Also, there was a slight drop in the yield when the loading of the catalyst was decreased (Table 11**,** entry 17). The decrease in the amount of the base from 2.0 mmol to 0.5 mmol or 1.0 mmol led to a decrease in the yield of product form 69% to 40% and 57 %, respectively (Table 11**,** entries 21-22). In addition, when the amount of the base was increased to 2.50 mmol, no significant improvement in the yield of product was observed (Table 11**,** entry 23). The catalytic activity of BOX-OH-1 was compared to some commercial compounds including 1,10-phenanthroline, 2,2'-bipyridine and N,N,N,N-tetramethyl-1,2-ethylenediamine (Table 11, entries 24-26). Although, all these ligands showed some relatively good activity, however, the catalytic activity of the catalyst system based on the new ligand BOX-OH-1 is to certain extent more active and highly reproducible (Table 11, entry 7) [39].

Table 11: C-H activation of benzene with 4-iodoanisole catalyzed by nickel complexes: Optimization of the reaction conditions.[a]



Entry	Nickel Catalyst (mmol)	Bases	Yield (%)[b]
1	$NiCl_2.6H_2O$ (0.1)	K_2CO_3 (4.0 equiv.)	-
2	$NiCl_2.6H_2O$ (0.1)	LiH (4.0 equiv.)	10
3	$NiCl_2.6H_2O$ (0.1)	K^tOBu (4.0 equiv.)	43
4	$NiCl_2.6H_2O$ (0.1)	Et_3N (4.0 equiv.)	-
5	$Ni(OAc)_2.4H_2O$ (0.1)	K_2CO_3 (4.0 equiv.)	Traces
6	$Ni(OAc)_2.4H_2O$ (0.1)	LiH (4.0 equiv.)	52
7	$Ni(OAc)_2.4H_2O$ (0.1)	K^tOBu (4.0 equiv.)	69
8	$Ni(OAc)_2.4H_2O$ (0.1)	Et_3N (4.0 equiv.)	-
9	$Ni(ClO_4)_2.6H_2O$ (0.1)	K_2CO_3 (4.0 equiv.)	-
10	$Ni(ClO_4)_2.6H_2O$ (0.1)	LiH (4.0 equiv.)	Traces
11	$Ni(ClO_4)_2.6H_2O$ (0.1)	K^tOBu (4.0 equiv.)	23
12	$Ni(ClO_4)_2.6H_2O$ (0.1)	Et_3N (4.0 equiv.)	-
13	$Ni(OTf)_2$ (0.1)	K_2CO_3 (4.0 equiv.)	-
14	$Ni(OTf)_2$ (0.1)	LiH (4.0 equiv.)	Traces
15	$Ni(OTf)_2$ (0.1)	K^tOBu (4.0 equiv.)	19
16	$Ni(OTf)_2$ (0.1)	Et_3N (4.0 equiv.)	-
17[c]	$Ni(OAc)_2.4H_2O$ (0.05)	K^tOBu (4.0 equiv.)	57
1b[d]	$Ni(OAc)_2.4H_2O$ (0.025)	K^tOBu (4.0 equiv.)	45
19[e]	$Ni(OAc)_2.4H_2O$ (0.1)	K^tOBu (4.0 equiv.)	Traces
20	$Ni(OAc)_2.4H_2O$ (0.1)	Nil	-
21[f]	$Ni(OAc)_2.4H_2O$ (0.1)	K^tOBu (1.0 equiv.)	40
22	$Ni(OAc)_2.4H_2O$ (0.1)	K^tOBu (2.0 equiv.)	59

23	$Ni(OAc)_2.4H_2O$ (0.1)	K^tOBu (5.0 equiv.)	70
24[g]	$Ni(OAc)_2.4H_2O$ (0.1)	K^tOBu (4.0 equiv.)	62
25[h]	$Ni(OAc)_2.4H_2O$ (0.1)	K^tOBu (4.0 equiv.)	59
26[i]	$Ni(OAc)_2.4H_2O$ (0.1)	K^tOBu (4.0 equiv.)	45

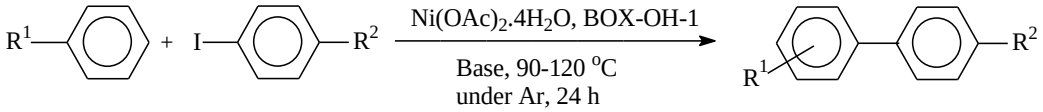
[a] Reaction conditions: [Ni] (0.10 mmol), BOX-OH-1 (0.20 mmol), 4-iodoanisole (0.50 mmol), base (2.0 mmol) in benzene (3 mL) under Ar, 90 °C, 24 h.
[b] Isolated yield relative to the 4-iodoanisole
[c] Nickel catalyst (10 mol%, 0.05 mmol), BOX-OH-1 ligand (20 mol%, 0.1 mmol)
[d] Nickel catalyst (5 mol%, 0.025 mmol), BOX-OH-1 ligand (10 mol%, 0.05 mmol)
[e] Nickel catalyst (20 mol%, 0.1 mmol), with no BOX-OH-1 ligand
[f] Solvent [DMF:H_2O] (0.5:0.5 mL)
[g] 1,10-Phenanthroline as a ligand
[h] 2,2'-Bipyridine as a ligand
[i] N,N,N,N-tetramethyl-1, 2-ethylenediamine as a ligand

Table 12 summarizes the results of the C-H arylation coupling reactions of different unactivated arenes with various aryl iodides using $Ni(OAc)_2.4H_2O$ and BOX-OH-1 in the presence of a strong base, K^tOBu, at 120 °C. The C-H activation by coupling aryl iodides having either electron releasing or electron withdrawing substituents was considered with different arenes (benzene, anisole and benzonitrile) (Table 12, entries 1-6). The results of the C-H activation coupling of 4-iodoacetophenone, an aryl iodide having an electron withdrawing substituent in para position, with benzene, a neutral arene, gave high yield (74%) (Table 12, entry 1). A lower yield (57%) was observed with 4-iodoanisole, an aryl iodide having an electron releasing substituent (Table 12, entry 2). Also, the C-H activation of the arene carrying an electron releasing group (anisole) was conducted with aryl iodides substituted with an electron withdrawing or electron releasing groups at the para positions. The reactions gave predominantly the para-regioisomers as the major products (67% and 54% of the total products, respectively) (Table 12, entries 3 and 4). The C-H activation of benzonitrile was carried out with 4-iodoacetophenone and 4-

iodoanisole. Both reactions gave poor yields (33% and 27%, respectively), where the meta-regioisomers were the major product of the coupling reactions (Table 12, entries 5 and 6).

In summary, the reactivity of the aryl iodides in the C-H activation of unactivated arenes under the optimized experimental conditions is very much affected by the substituents on the aryl iodides: substrates with the electron withdrawing groups are more reactive than those with electron releasing substituents. The reactivity is also affected by the type of substituent on the arene: the neutral arenes are more reactive than the arenes with electron releasing groups, which are more reactive than the arenes with electron withdrawing substituents.

Table 12: Nickel-salt/BOX-OH-1catalyzed C-H arylation of unactivated arenes coupling reaction with aryl iodides.[a]



Entry	R^1	R^2	Yield (%)[b]
1	H	*p*-C=O(CH_3)	74
2	H	*p*-OCH_3	57
3	OCH_3	*p*-C=O(CH_3)	67
4	OCH_3	*p*-OCH_3	54
5	CN	*p*-C=O(CH_3)	33
6	CN	*p*-OCH_3	28

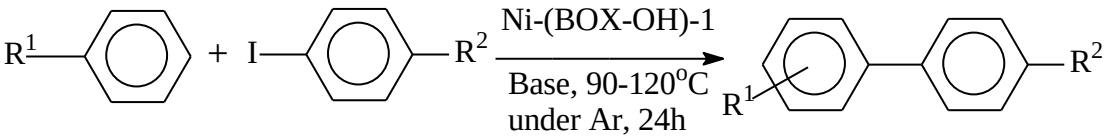
[a] Reaction conditions: $Ni(OAc)_2.4H_2O$ (0.10 mmol), BOX-OH-1 (0.20 mmol), aryl iodide (0.50 mmol), K^{t}OBu (4.0 equiv.) in arene (2 mL) under Ar, 90-120 °C, 24 h.

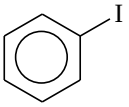
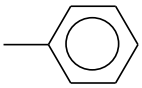
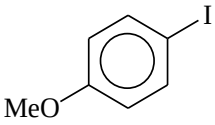
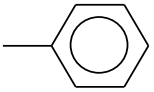
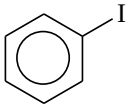
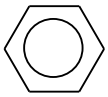
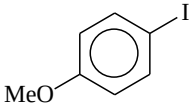
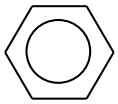
[b] Isolated yield.

The nickel complex Ni-(BOX-OH)-1 was also considered in the C-H arylation of unactivated arenes coupling reactions with aryl iodides. The results are summarized in the Table 13.

The coupling reaction of iodobenzene and 4-iodoanisole with toluene gave almost similar yields (46-48%) of products (Table 13, entries 1 and 2). The reaction of iodobenzene with benzene gave higher yield of product (70%) (Table 13, entry 3), while the reaction of benezene with 4-iodoanisole gave moderate yield (54%) (Table 13, entry 4) and 4-iodoanisole (Table 13, entry 4).

Table 13: Nickel-BOX-OH-1catalyzed C-H arylation of unactivated arenes coupling reaction with aryl iodides.[a]



Entry	Aryl iodide	Arene	Yield (%)[b]
1			48
2			46
3			70
4			54

[a] Reaction conditions: Ni-BOX-OH-1 (20 mol%), aryl halide (0.5 mmol), KtOBu (4.0 equiv.) in arene (3 mL) in Ar at 90-120 °C for 24 h.
[b] Isolated yield.

CHAPTER 5

PALLADIUM(II)-BOX-OH-1 CATALYZED CARBONYLATIVE COUPLING REACTIONS

Heck and his coworkers were among the pioneers to report palladium-catalyzed carbonylation in the 1970s [113-114]. Alkoxycarbonylation, aminocarbonylation, double carbonylation and oxidative carbonylation are the major types of carbonylation reactions that have received considerable attention in the last decade. However, the most common carbonylation reactions are alkoxycarbonylation and aminocarbonylation of aryl halides. These reactions are efficient methods for the synthesis of amides and esters with palladium-catalyzed catalytic systems using aryl halides and alkynes as substrates. Several homogeneous and heterogeneous palladium catalyzed catalytic strategies have been established for the synthesis of these valuable products [118, 127-128]. Paraformaldehyde, as the source of carbon monoxide, has been considered for alkoxycarbonylation in order to avoid the toxicity of typical CO gas, which many synthetic organic chemists consider as a disadvantage. Hence, a number of aryl bromides have been converted successfully to desirable aromatic aldehydes and esters with appreciable yields.

5.1 Experimental

All the chemicals and materials used to carry out these carbonylation reactions were of high purity as they were all used as purchased from the respective chemical companies. We were careful to make sure that all the solvents employed for the reactions were in their anhydrous forms. A GC-FID instrument was used to analyze the products of the carbonylation reactions. The mixture of product was further separated by using flash column chromatography technique with 60F Silica gel from Fluka Chemie AG (Buchs, Switzerland).

5.1.1 General procedure for alkoxycarbonylation of iodobenzene

Pd-(BOX-OH)-1 (0.020 mmmol), an alcohol (5.0 mL), iodobenzene (1.0 mmol) and KOH (2.0 mmol) were placed in a dry clean glass liner containing a magnetic bar for stirring. The glass liner was then placed in an autoclave which was closed tightly and purged three times with CO to release the air it contains, and then pressurized with 100 psi of CO gas. The autoclave was heated for 110 °C. Ethyl acetate (5 x 3 mL) was used to extract the product and purified by adopting diethyl ether and ethyl acetate as a solvent system using column chromatography with silica gel.

5.1.2 General procedure for aminocarbonylation of iodobezene

Pd-(BOX-OH)-1 (0.020 mmol), an amine (5 mL), iodobenzene (1.0 mmol) and KOH (2.0 mmol) were placed in a dry clean glass liner containing a magnetic bar for stirring. The clean glass was then placed in an autoclave, which was closed tightly, and purged three times with CO to remove the air, and then and pressurized with 100 psi of CO gas. The

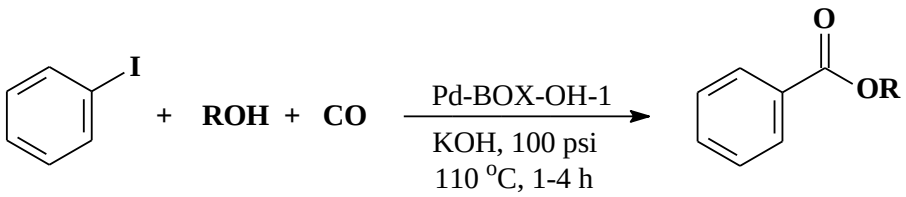
autoclave was heated at 110 °C. Ethyl acetate (5 x 3mL) was used to extract the product and then purified with hexane and ethyl acetate as a solvent system using column chromatography with silica gel.

5.2 Results and Discussions

5.2.1 Alkoxycarbonylation of iodobezene

The catalytic activity of the Pd-(BOX-OH)-1 was evaluated in alkoxycarbonylion of iodobenzene under the optimized reaction conditions. The reaction was conducted under CO pressure at 110 °C for 1-4 h. The results of the alkoxycarbonylation reactions of iodobenzene with various alcohols are summarized on the table 15. The reactions of primary and secondary alcohols were complete after 1 h, while the tertiary and aromatic alcohols required 4 h. The alkoxycarbonylation of iodobenzene with primary alcohols gave excellent yields (90 % and 96 %) (Table 14, entries 1 and 2). The secondary alcohol gave a very good yield (87 %) (Table 14, entry 3). However, the bulkier substrate such as tert-butyl alcohol gave lower yield (79 %) even after 4 h of reaction (Table 14, entry 4). Interestingly, phenol was more reactive and gave a higher yield (92%) of ester (Table 14, entry 5). In summary, the primary alcohols were more reactive than secondary and much more reactive than tertiary alcohols.

Table 14: Alkoxycarbonylation of iodobenzene.[a]



Entry	R	Yield (%)[b]
1	CH_3	96
2	$(CH_2)_2CH_3$	90
3	$(CH_3)_2CH$	87
4[c]	$(CH_3)_3C$	79
5[c]	C_6H_5	92

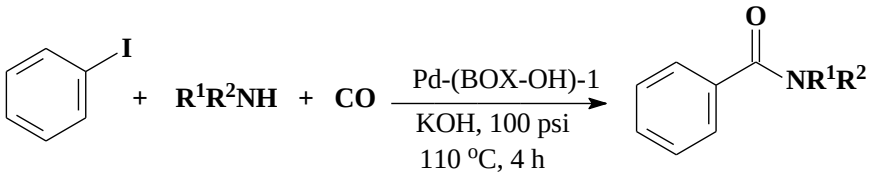
[a] Reaction conditions: Pd-(BOX-OH)-1 (0.020 mmol), iodobezene (1.0 mmol), alcohol (5 mL), KOH (2.0 mmol), 110 °C, 1 h.
[b] Isolated yield
[c] 4 h

5.2.2 Aminocarbonylation of iodobenzene

The catalytic activity of the Pd-(BOX-OH)-1 was also evaluated in aminocarbonylation of iodobenzene under the optimized reaction condition. The reactions of the aminocarbonylation of iodobenzene with various primary and secondary amines were conducted under CO pressure at 110 °C for 4 h and the results were summarized on Table 16. Excellent yield (96%) was obtained with methylamine as a primary amine (Table 16, entry 1), however, the secondary amine gave lower yield of amide under the same experimental conditions (Table 16, entry 2). The aminocarbonylation of iodobenzene in the presence of aniline and benzyl amine produced very good yields of amides (85% and

89% respectively) (Table 16, entries 3 and 4). The use of dibenzylamine led to relatively good yield (70%) (Table 16, entry 5) but lower as compared to other amines. According to the results obtained in this study, the aliphatic amines show better reactivity than the aromatic substituted amines, which relates probably to the higher steric hindrance on the nitrogen atoms.

Table 15: Aminocarbonylation of iodobenzene.[a]



Entry	R^1R^2NH	Yield (%)[b]
1	CH_3NH_2	96
2	$[(CH_3)_2CH]_2NH$	79
3	$C_6H_5NH_2$	85
4	$C_6H_5CH_2NH_2$	89
5	$[C_6H_5CH_2]_2NH$	70

[a] Reaction conditions: Pd-(BOX-OH)-1 (0.020 mmol), iodobenzene (1.0 mmol), Amine (5 mL), KOH (2.0 mmol), 4 h, 110 °C.
[b] Isolated yields.

CHAPTER 6

CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

The synthesis and characterization of novel bis(oxazoline)s and oxazoline compounds (BOX-OH-1, BOX-OH-2, OX-COOH, and Pyr-OX-OH) was successfully carried from the appropriate aminoalcohols and phthalonitrile or its derivatives and using the appropriate analysis techniques.

Also, the synthesis and characterization of novel palladium and nickel bis(oxazoline) complexes including Pd-(BOX-OH)-1, Pd-(BOX-OH)-2, and Pd-Pyr-(OX-OH), Ni-(BOX-OH)-1, Ni-(BOX-A) were achieved successfully and in excellent yields. The palladium complex, Pd-(BOX-OH)-1 , was also characterized by X-ray crystallography while no crystals suitable for X-ray crystallography were obtained for other palladium complexes [Pd-(BOX-OH)-2, Pd-Pry-(OX-OH)], and nickel complexes [Ni-(BOX-A), Ni-(BOX-OH)-1]. In addition, the new nickel complexes were characterized using only FTIR and elemental analysis. Their paramagnetic nature makes them difficult to be characterized by NMR.

Furthermore, the catalytic activity of the new palladium complexes was evaluated in cross coupling reactions including Suzuki-Miyaura, Mizoroki-Heck, and Sonogoshira reactions. Excellent results were obtained in neat water and in water-organic solvent which made these complexes as green and highly efficient catalysts.

The catalytic performance of the palladium complex Pd-(BOX-OH)-1 was also evaluated in alkoxycarbonylation and aminocarbonylation of aryl iodides. Different aryl esters and amides were produced in high yields.

Finally, the catalytic activity of the nickel complex [Ni-(BOX-OH)-1, Ni-(BOX-A)] was assessed in direct C-H arylation reactions of arenes with aryl iodides. Very good yields of biaryls and substituted biaryls were obtained.

In summary, new palladium and nickel bis(oxazoline) catalysts were designed, synthesized and carefully evaluated in different cross coupling, carbonylative coupling and C-H arylation reactions.

6.2 Recommendations

1. Other more water soluble BOX-OH ligands should be synthesized and different metal complexes should be developed for better catalytic activity in aqueous medium.
2. The role of solvent in the reaction should be investigated and the mechanism of the Suzuki-Miyaura coupling reaction in aqueous medium reaction should be carefully studied.
3. New water soluble Pd-(BOX-OH)-PR_3 catalysts should be developed for the cross coupling reactions of aryl bromides and aryl chlorides that are more difficult as compared to aryl iodides.
4. New and more active nickel catalysts should be developed for the C-H activation reactions and the mechanism of the reaction should be carefully studied to identify the role of the ligands in the reaction.
5. Heterogeneous M-(BOX-OH) catalysts, including palladium-, nickel-, copper-, rhodium-, iridium-, cobalt- and iron-(BOX-OH), should be developed for different organic transformations.

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